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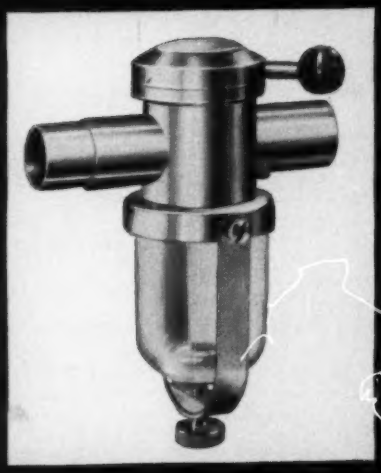

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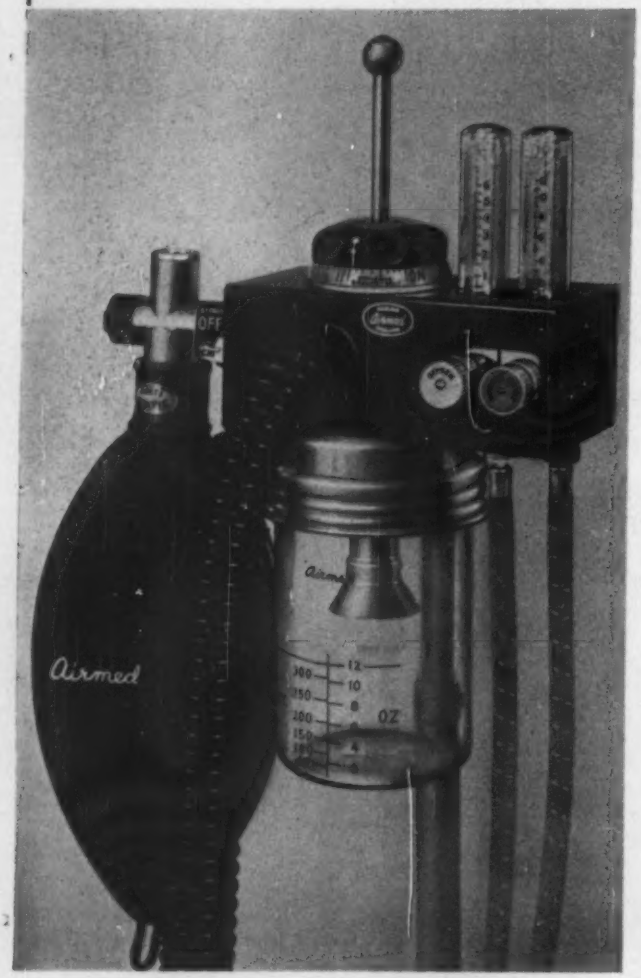

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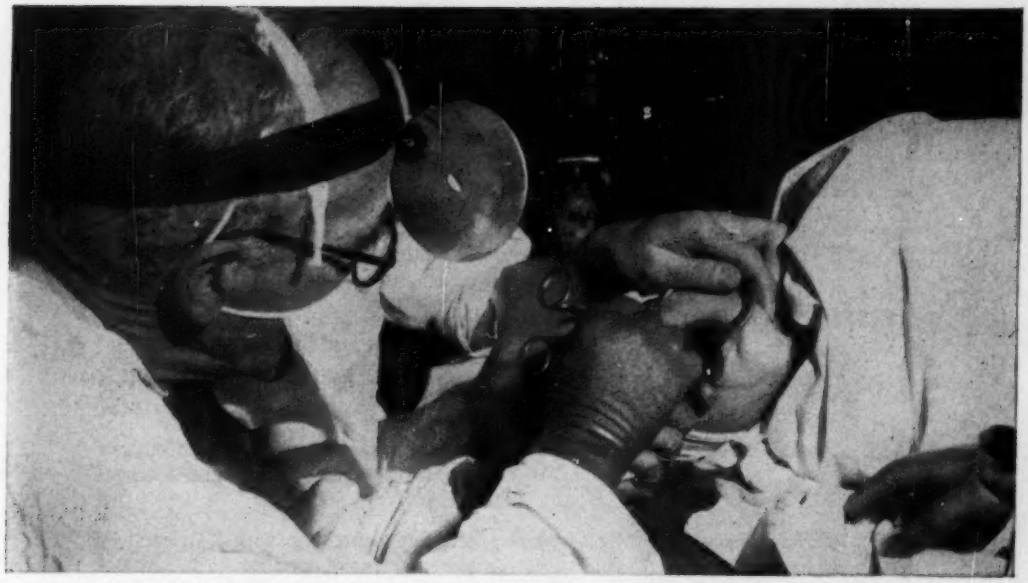

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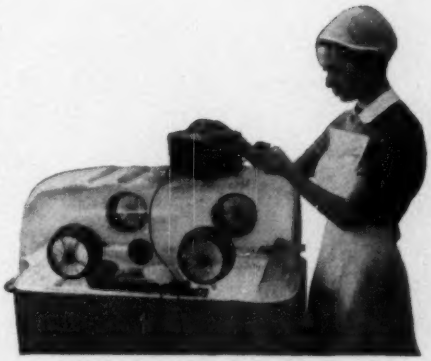

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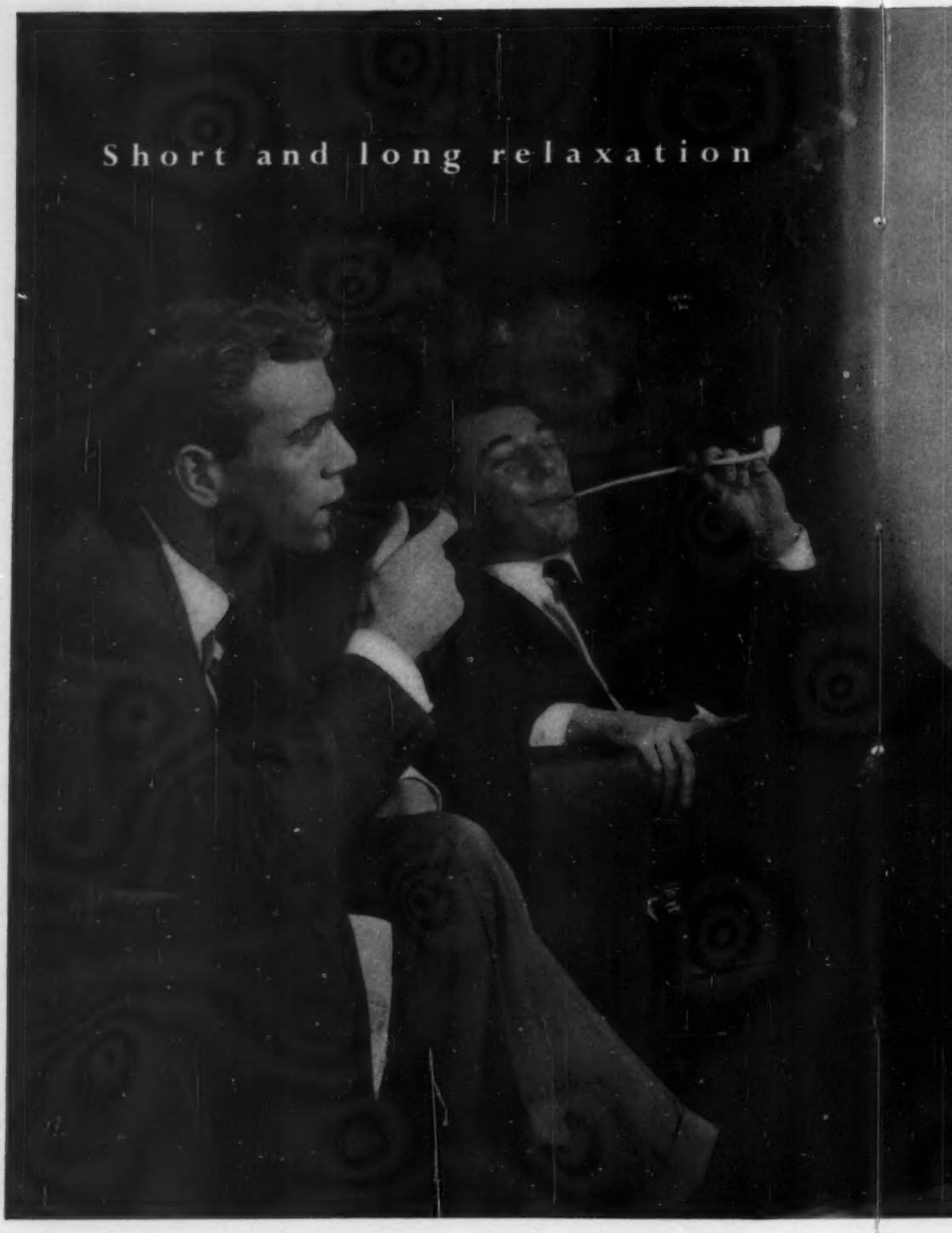
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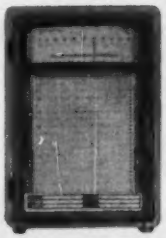

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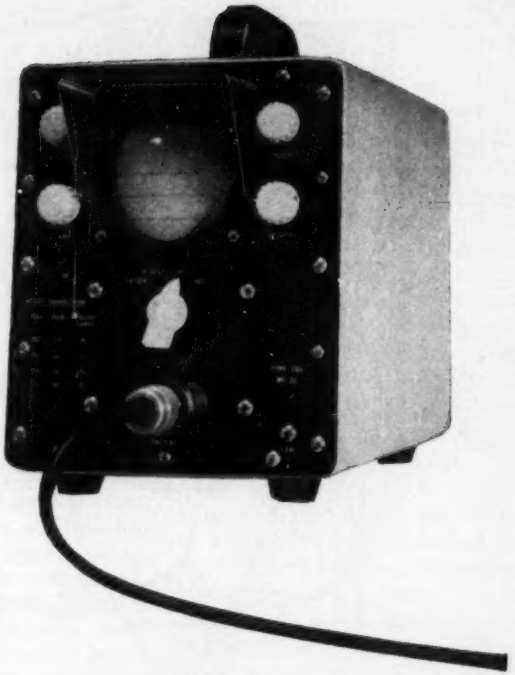

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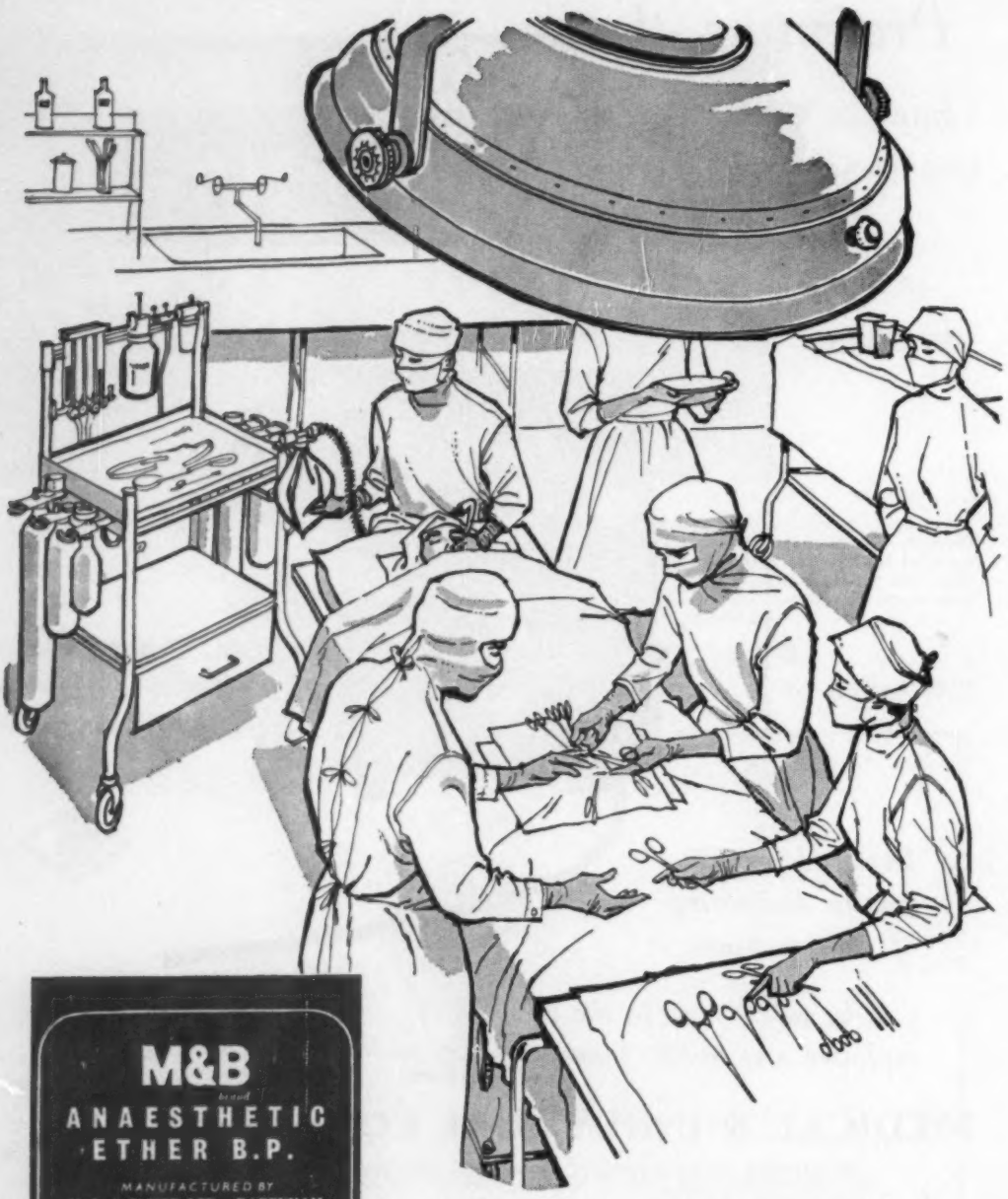

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BRITISH JOURNAL OF ANAESTHESIA

VOL. XXXII, No. 2 FEBRUARY 1960

EDITORIAL

A SIGN OF PROGRESS

Years ago when a surgeon was doubtful of the advisability of operating on a patient he frequently asked a physician to see the patient and express his opinion. The idea presumably was to obtain moral support. The request was very usually put in this form: "Mr. X would be pleased if Dr. Y would tell us if this patient is fit to stand an anaesthetic"—the operation itself apparently being a mere trifle and if the patient was so foolish as to die after it, well that was his own fault. All that modern surgery could do had been done and it could not be blamed for so unfortunate a result.

The absurdity of this proceeding never seemed to strike the surgeon or the physician concerned, yet a moment's reflection would have revealed it. Years before the physician had grown to his present eminence, when indeed he was an undergraduate, he was signed up as having given the required number of anaesthetics. In later years, when the importance of anaesthetics was beginning to be recognized, the official number in some of the more up-to-date hospitals was twenty. Owing to some slackness on the part of the official responsible for signing up students it was quite certain that a number of them got through without completing the full list. Some of us heard not so long ago that one well-known professor of anaesthesia was signed up when he had only given one, and though this particular gentleman has since then made ample amends for this early delinquency, had he become a physician that anaesthetic would in all probability have been not only his first but his last. It is to such a man that the surgeon used to enquire as to the fitness of his patient to receive an anaesthetic.

Surgical operations are so much more numerous today than formerly and are undertaken with a lightheartedness that would have been impossible years ago. The majority of patients coming to operation are in good health and require very little in the way of preliminary examination. There are a number, however, to whom an expert and adequate preliminary examination is a matter of life and death; without it they die, properly prepared they live. It is not, however, to a physician that application is made but to the biochemistry and haematological clinical laboratories for a knowledge of the electrolytes, the blood urea, the blood sugar, the ventilatory capacity of the patient, etc. When the condition of the patient in these respects has been ascertained and deficiencies remedied as far as possible, then, and only then, is the patient ready for operation and in the best position to survive the operation and the anaesthetic.

Such is the training of the modern anaesthetist who aspires to consultant status that he should be able to interpret the mass of data supplied to him by these auxiliary agencies, and apply them to the immense benefit of his patient.

Brit. J. Anaesth. (1960), 32, 48

A METHOD FOR ASSESSING THE EFFICACY OF ORAL ANALGESICS: ITS APPLICATIONS AND LIMITATIONS

BY

JOHN W. DUNDEE

Department of Anaesthetics, Queen's University of Belfast, Northern Ireland

THE magnitude of the unsolved problems in the measurement of pain is best illustrated by reference to the size of Beecher's (1957) recent review on this subject. This occupied 150 journal pages and quoted 701 references. It is not proposed to discuss this subject in detail, but simply to refer to data pertinent to this publication. Measurement of experimental pain is very limited in its clinical applications because of lack of correlation between the findings with the various techniques and those obtained with pathological pain.

Postoperative pain provides a good field for the evaluation of new analgesics and has been used by Denton and Beecher (1949) and others. These workers remark that "the accurate appraisal of new narcotics is so time consuming that it should not be undertaken by the busy practising clinicians who are burdened with other responsibilities, but by investigators who can devote their entire attention to it". They suggest, however, that patients with terminal cancer would provide a more suitable group of subjects for the study of both analgesic power and side action potency. Such a group of patients has been available to the author, at a clinic for the symptomatic relief of chronic pain (Dundee, 1957). However, the criteria set out by Denton and Beecher as regards fulltime investigators could not be met in the available circumstances.

Little attention is paid in the literature to the evaluation of oral analgesics, yet these drugs are more widely used than parenteral therapy in patients who are not hospitalized and offer the only available hope of pain relief to cases of malignancy. It is felt that this field deserves more attention than has been given to it in the past and for this reason the method to be described has been evolved.

Rather than attempt an evaluation of the degree of pain which patients suffered before and after their analgesic, they were asked to grade the relief obtained. This was of great psychological importance as the word "pain" was rarely mentioned during conversations with the patient. It has also been possible to study the comparative toxicity of various agents at the same time as evaluating the analgesics.

METHOD

Patients were seen at intervals not exceeding two weeks, the majority attending weekly. It was explained to them that an attempt would be made to find an appropriate dose of a suitable drug which would relieve their pain with the minimum upset, and that this might necessitate the trial of two or more drugs or alterations in dosage of the same drug. The necessity for their co-operation was stressed. It was emphasized that they alone could assess the benefit received from a particular drug, and that only on their recommendation would the final treatment be decided.

When the analgesics to be studied were decided upon the patient was given two boxes of drugs labelled "A" and "B", with appropriate instructions as to their frequency of administration which was always the same for any pair of drugs. Occasionally when they could not be seen for two weeks three drugs were given. In most instances one of these three drugs was an inert placebo. Each drug was taken for at least three days, unless the severity of side effects precluded such prolonged administration. When a placebo was used in the trial its administration was most commonly interspersed between that of two active drugs. As far as possible the order of administration of the standard drug and the preparation under trial was randomized over the series of cases concerned.

It will be appreciated that all the drugs used in such trials must be personally dispensed to the patients and that a prescription is useless. By

courtesy of various firms, "multidose" tablets were made available, containing three times the contents of the standard commercial preparations (e.g. for methadone the standard tablet contains 5 mg, whereas the "multidose" tablets contained 15 mg). This meant that no patient was ever asked to take more than two tablets to achieve the desired dose. This is very important as, on more than one occasion, patients objected to taking large numbers of "standard" dose tablets, yet reacted favourably when two "multidose" tablets, having the same total dosage, were given. Likewise, when trying out analgesics and antiemetic drugs, a combined tablet was most valuable.

Patients were given two forms. One of these outlined what was required of them—the frequency of administration and number of tablets to be taken, the time and date of their next appointment—and stated that without their fullest co-operation, the trial would be useless. The other was, in effect, a day-to-day diary in which to record their reactions to the drugs over a period of one week. The information which they were asked to record was explained to them in as simple language as possible and the form listed all possible side effects which they were likely to encounter. They were instructed to complete the appropriate section each day and not to leave it all to the end of the week when they were due to return to the clinic.

The nature, dosage and number of the drugs issued was entered into each patient's case record, but the key to the identity of A, B, etc., was recorded separately. When the patients returned, their completed forms were studied, they were questioned on their data and the appropriate score of analgesia and toxicity (table I) was decided without knowing the nature of the drugs taken.

Ideally the assessment of the action of the drugs should be made by a person other than the one who dispensed the drugs. The final assessment of scores was invariably made by the author to eliminate "observer error" as to grades of analgesia and lack of toxicity. Arranging for the dispensing to be done by someone other than the observer was often difficult, since the help of a colleague was not always available. Where a colleague of sufficient seniority did not order the treatment, this was done by the author, but the allotment of the appropriate letter and the dispensing of the drugs was left to a registrar or senior house officer. On a few occasions when recording the effects of the drugs, it was impossible to eliminate bias completely, as the patients would refer to the tablets by their size, colour, shape or the pattern stamped on them. The levorphanol tartrate (Dromoran) 1.5 mg tablet with its concentric rings, was most frequently the cause of this trouble. To overcome this, in trials of new drugs, manufacturers were asked to prepare a large variety of identical tablets containing both the new preparation and standard preparations with which it could be compared and an identical inert placebo tablet. There was no means of getting over this problem when commercial preparations of available drugs were compared.

TABLE I

Scheme for scoring for pain relief and lack of toxicity.

Score	Analgesia	Lack of toxicity
5	Excellent	No side effects.
4	Good	Slight nausea, vomiting, constipation, drowsiness or dizziness.
3	Moderate	Two or more side effects—not very troublesome.
2	Poor	Troublesome side effects—tolerable.
1	Doubtful or nil	Side effects of such severity as to necessitate stopping drugs.

SELECTION OF PATIENTS

Intelligence and co-operation were not the only requirements of patients in whom the action of different analgesics is to be accurately compared. Experience with the method described above has shown that, with a few exceptions, better results will be obtained in patients with pain due to malignancy than in those suffering from benign conditions. This latter group is largely composed of patients with pain of very long duration and frequently of doubtful aetiology. Some of these might have personality changes and be classed as suffering from "psychogenic" pain and the likelihood of any general analgesic producing adequate pain relief in these cases is usually remote. Their record of the effects of the same analgesic is very inconsistent and the same drug

given on more than one occasion may have a completely different action. The side effects reported by these patients are often more imaginary than real and are likewise inconsistent.

With pain of neoplastic origin one has to be certain that the intensity and nature of the pain is not likely to alter over the period of the trial, and results obtained over a two- or three-week period must be regarded with suspicion. It is not always possible to foresee an alteration in the intensity of pain, but it can always be detected at the end of the trial. When such a change has occurred the results obtained must be discarded.

The problems arising from acquired tolerance to analgesics and from addiction must also be considered in relation to the selection of patients for drug trials. It has become very obvious to the author that acquired tolerance to any of the analgesics induces cross tolerance to any of the other drugs of similar potency. The development of tolerance varies greatly from patient to patient. As a usual rule it is slowly acquired at first, but, once a marked increase in dosage becomes needed, the tolerance increases rapidly and the dose can be frequently doubled or trebled over a two- to three-weeks period, without any increase in the resulting analgesia, but sometimes with a higher incidence and severity of side effects. Even if tolerance has developed in a subject, as long as the results with a given drug are not compared with those of another drug given three or four weeks later, acquired tolerance does not invalidate this method of comparing oral analgesics.

Addiction to analgesics may exist and yet not be apparent when a patient is first seen. As a general rule, addicts do not record a high incidence of severe side effects (otherwise they would not be able to continue taking the drugs), but the sudden development of toxic symptoms with a new drug or a placebo immediately makes one suspicious. These toxic manifestations may well be withdrawal symptoms. The importance of this is best shown by two actual examples.

When dihydrocodeine (DHC) first became available for clinical trial, all the patients who were getting relief from potent analgesics were given a supply. The results obtained varied from good pain relief with no side effects to complete absence of relief with nausea, vomiting, sweating, palpitations, tremor, insomnia and anorexia as toxic manifestations. There was no obvious relationship of dosage to the side effects. Increasing experience with DHC showed it to be a drug with a low addiction potential and when given to known addicts it almost always produced some degree of withdrawal symptoms.

A combination of levorphanol tartrate (Dromoran) and levallorphan (Lorfan) was once tried as an analgesic. The variability of results was identical with those obtained with DHC and it was eventually shown that the levallorphan in the mixture would produce withdrawal symptoms in addicts to D.D.A. analgesics.

Known addicts are not used in the comparison of new analgesics, but are invaluable for finding out whether a new compound is likely to cause addiction. The great difficulty lies in discovering which patients actually are addicts, and here neither the data on dosage nor the duration of the administration of D.D.A. drugs is likely to be of help. There is a type of patient who will develop a craving and physical dependence on a drug within ten days, while with another type the same drug can be discontinued without any side effects after a period of administration lasting up to two years. This individual susceptibility has been stressed by Batterman (1948), Isbell (1948) and others. Here the use of the identical placebo tablet is of great value. A higher incidence of side effects after the inert tablet than after the active analgesic is highly suggestive (but not definite proof) of some degree of drug addiction. A fallacy in this test is revealed by the patient with severe pain of organic origin who is getting good relief from a given drug and who, when given an inactive placebo or less potent drug, will record untruthfully severe toxic effects from the new preparation, as a safeguard against a change in what has proved to them to be a satisfactory form of treatment. While not strictly falling into the category of true addicts in whom, according to Isbell (1948), both physical and emotional dependence should be present, these cases must be treated as potential addicts.

Based on his observations on the enhanced effect of placebo in stress, Beecher (1956) has suggested that therapeutically active drugs may be proportionately more effective with increasing stress. During this work it has been found that patients in severe pain and mental anguish

(mostly due to malignancy) who have seen a number of doctors (e.g. radiotherapists, surgeons, neurologists) each having a different approach to their malady and yet not contributing anything to their pain relief, form by far the best subjects for a therapeutic trial of analgesics. It is relevant that Cleghorn and his colleagues (1950) found that an increase in anxiety was accompanied by a greater adrenocortical response to a placebo injection.

RELATIONSHIP OF ANALGESIA TO TOXICITY

Strictly speaking, the analgesic action and toxicity are two distinct properties of a drug and in a nonclinical pharmacological study would be considered separately. However, this method records the patient's response to the analgesic and there is a distinct correlation between these two facets of drug action (table II: the data in this table is from the first 750 observations with this method in patients with pain from a variety of causes). The correlation is also partly due to the use of the oral route for administration of the drug; patients who vomit the tablets could not be expected to get any appreciable pain relief. It can also be seen that with a low analgesic score there is a fairly even distribution of the incidence of various grades of side effects.

TABLE II

Relationship between analgesic score and lack of toxicity score, etc.

Lack of toxicity	Analgesia 5	4	3	2	1	Total
5	88	83	62	40	33	306
4	24	32	41	28	11	136
3	28	30	52	27	21	158
2	13	11	19	20	18	81
1	10	9	8	13	29	69
Total	163	165	182	128	112	750

A marked relationship ($P<0.01$; χ^2 79.76; df 16) was found between these factors.

In interpreting the data with any two drugs, it is important to remember that patients are more likely to record a high analgesic score with doses which have none or few side effects and that a high degree of toxicity usually results in a low grade of analgesia. Otherwise one might attribute greater potency than is justifiable to the weaker analgesics which have few side effects.

OPTIMAL AND SUPRA-OPTIMAL DOSAGE

It is not always appreciated that the maximum possible degree of analgesia with minimum side effects can frequently be achieved with a moderate dose of analgesic. Increasing this dose gives a negligible improvement in the analgesia and usually results in a greater incidence and severity of side effects. Lasagna and Beecher (1954) have shown that 10 mg of morphine per 70 kg of body weight represents an optimal dose, taking into account the very rapid increase in toxic effects produced when this dose is exceeded and the fact that there was only about a 10 per cent increase in pain-relieving power when this dose was increased to 15 mg. Although, in the method of assessing pain relief described above, dosage is not calculated on a weight basis, on many occasions this phenomenon has been observed with large doses of analgesics. It will be reported more fully in another publication (Dundee, 1959). By virtue of the influence of side effects on the patient's evaluation of analgesic action, supra-optimal doses may be recorded as being less efficacious and this must be borne in mind when analyzing results.

PLACEBOS

Reference has already been made to the use of the inert placebo tablet in detecting potential addicts. Many workers are firmly convinced of the therapeutic value of a placebo in relieving pain and Beecher (1955) reported that it produced relief in 32.5 per cent of patients. Early in this work the placebo was widely used and it was originally intended that the analgesic score should be "corrected" by subtraction of the placebo score. This plan was never practical; the vast majority of cases with severe pain due to malignancy recorded negligible, if any, pain relief from the inert tablet over the three-day period of its administration (table III).

The number of observations from placebos in patients with pain not due to malignancy is very small, but is reported fully in table IV for comparison with the data in table III. When these two tables are compared (using the scheme for pooling of scores to be described later), it is found that patients with pain due to malignancy obtained significantly less benefit from the placebo ($P<0.001$; $\chi^2=16.68$; $df=2$) than the

other cases. The incidence of side effects was the same for both groups ($0.10>P>0.05$; $\chi^2=3.37$; $df=1$).

TABLE III

Scores in patients with pain from malignant disease following use of a placebo.

Freedom from toxicity	"Analgesic" score					Total
	5	4	3	2	1	
5	0	5	8	10	104	127
4	5	0	0	0	27	32
3	0	5	5	0	9	19
2	0	0	0	0	2	2
1	0	0	1	1	0	2
Total	5	10	14	11	142	182

TABLE IV

Scores in patients with pain of non-malignant aetiology following use of a placebo.

Freedom from toxicity	Grade of analgesia					Total
	5	4	3	2	1	
5	0	2	2	2	5	11
4	2	1	0	1	5	9
3	0	0	5	0	0	5
2	0	0	1	0	0	1
1	0	0	0	0	1	1
Total	2	3	8	3	11	27

This data throws doubt on the universal use of the placebo tablet in the study of the efficacy of oral analgesics. The author now reserves its use for the following circumstances:

(*a*) Detection of possible drug addicts.

(*b*) In patients with pain which might be psychogenic in origin especially where the analgesic score, from what is considered to be an effective dose of a strong analgesic, is less than expected.

(*c*) In any patient who reports a high incidence of side effects. Occasionally one finds that any tablet (active or inert) will cause nausea and vomiting in some patients. Where the toxic effects of an analgesic have been very marked, a few days respite from these, during the administration of a placebo, often helps to restore the patient's confidence in the hope that a nontoxic effective drug (or combination of drugs) can be found to suit their particular malady.

It is no longer felt justifiable as a routine procedure to subject patients with severe pain to the use of an inactive tablet.

One can only speculate on the difference between the effects of a placebo as reported above and the published findings of Beecher (1955). In Beecher's study, all drugs were given by injection to hospitalized patients suffering from post-operative pain. One can postulate that the psychological effect of an injection is greater than that of the oral self-administration of a tablet in the patient's own home.

GROUPING OF SCORES

With five possible grades of analgesia and toxicity a large number of observations is necessary before the effects of any two drugs can be compared statistically using the chi-squared method. This can be overcome by pooling two scores, bearing in mind that this grouping must have a clinical basis. The following has proved satisfactory in practice.

A—Analgesic score:
- Good relief — Scores 5 and 4.
- Moderate relief — Scores 3.
- Poor relief — Scores 2 and 1.

B—Lack of toxicity:
- No side effects — Scores 5.
- Slight side effects — Scores 4 and 3.
- Severe side effects — Scores 2 and 1.

One might even suggest scoring the results only on the above groupings in the first instance, thereby simplifying matters. However, this will not allow minor differences between drugs to be detected and will render calculation of the "Efficacy of the Analgesic" (to be discussed later) impossible.

STATISTICAL HANDLING OF DATA

The actions of two drugs can be compared by the chi-squared method of analysis, since the data is not sufficiently quantitative for the analysis of variance technique. The procedure adopted will depend on the number of observations available, and analgesia and toxicity are always considered separately. With large numbers, the score for the second drug will be compared with the score for the first using the 5×5 table. If numbers are not sufficient, grouping of scores

will be needed as shown above and a 3×3 table is used. If one drug is markedly superior to the other there will be too many cells with zero readings to allow a 5×5 or 3×3 table to be subjected to statistical evaluation and the scores for each drug can then be compared directly (5×2 or 3×2). An example illustrating this is given in the appendix.

COMBINED SCORES

Since the toxicity aspect is scored in reverse of the severity of the side effects (the most side effects and the smallest analgesic effect gives the lowest score and vice versa), it was originally planned to add the analgesic score (Sa) and the score for freedom from toxicity (St) thus arriving at a figure which would give some idea of the efficacy of the analgesic (E). The fallacy of this argument soon became apparent since $Sa=3$ and $St=2$ would give the same factor for E as one would get with a completely ineffective non-toxic drug or an effective drug of such toxicity as to be of no clinical use.

The following formula is now recommended:

$$E=(Sa \times St)-5$$

The subtraction of 5 from the product (e.g. $Sa=5$, $St=1$ or vice versa) ensures a negative or zero score for any dose of a drug which is of no clinical value, whether this be due to toxicity or lack of potency.

It must be realized that the same statistical importance must not be attached to E as to the chi-squared technique described in the preceding section. At the most, it gives a quick method of seeing whether any given study is likely to give any worthwhile results, and it must not be used as the sole criterion for deciding the merits of a given drug.

REPRODUCIBILITY OF READINGS

The crucial test of any method for assessing analgesia is the ability to produce comparable data with the method on more than one occasion. This is discussed in some detail. For various reasons, mostly involving acquired tolerance, it was difficult to obtain such data with this method in a large number of suitable patients. However, by combining the results with a variety of drugs, which were scored on more than one occasion, 176 observations were available for analysis. It was necessary to divide these patients into three groups as shown in table V and, as far as possible, to consider each group separately.

TABLE V

Groups of patients in whom the score for analgesia and lack of toxicity were compared on two occasions.

Group A (44 cases)	Highly intelligent and co-operative patients. Ten days maximum interval between two administrations. No other drugs being given. Pain mostly due to malignancy but patients' condition unchanged over period of observation. No placebo reactors.
Group B (52 cases)	Patients receiving analgesics alone, but not fulfilling above criteria. Maximum time between administrations was five weeks. Pain from a variety of causes.
Group C (80 cases)	Patients receiving combinations of analgesics and adjuvants. All available data grouped together (because of small numbers, subdivision as for patients receiving analgesics alone was not feasible).

Table VI shows the analgesic scores for each series, while table VII groups these series for the purposes of statistical evaluations. The results of series A need no statistical analysis to demonstrate the similarity of the scoring on the two occasions.

TABLE VI

Data on analgesic score from the same dose of analgesic administered to patients on two occasions.

Group	Second administration	First administration 5	4	3	2	1	Total
A	5	10	1	–	–	–	11
	4	–	6	1	–	–	7
	3	–	1	13	1	–	15
	2	–	–	1	4	–	5
	1	–	–	–	–	6	6
	Total	10	8	15	5	6	44
B	5	9	4	–	2	–	15
	4	2	5	3	–	–	10
	3	2	–	5	4	–	11
	2	1	2	1	2	2	8
	1	–	–	1	–	7	8
	Total	14	11	10	8	9	52
C	5	19	8	–	1	–	28
	4	3	8	4	–	–	15
	3	2	–	6	4	–	12
	2	–	2	2	3	2	9
	1	–	–	–	2	14	16
	Total	24	18	12	10	16	80

In the pooled data from B and C (table VII), the relationship between the degree of analgesia on each occasion is highly significant ($P<0.001$; $\chi^2=90.32$; $df=4$).

TABLE VII

Grouping of analgesia scores of data from table VI, according to arrangement described in table V.

Group	Second administration	First administration: Good (5&4)	Moderate (3)	Poor (2&1)	Total
A	Good	17	1	–	18
	Moderate	1	13	1	15
	Poor	–	1	10	11
	Total	18	15	11	44
B & C	Good	58	7	3	68
	Moderate	4	11	8	23
	Poor	5	4	32	41
	Total	67	22	43	132

TABLE VIII

Comparison of toxicity scores at two successive administrations of the same analgesic or analgesic-anti-emetic combination. Groups B and C are pooled because of the similarity of their figures and conditions pertaining to the observations.

Group	Second administration	First administration: 5	4	3	2	1	Total
A	5	16	1	–	–	–	17
	4	1	3	3	1	–	8
	3	–	1	13	3	–	17
	2	–	–	–	2	–	2
	1	–	–	–	–	–	–
	Total	17	5	16	6	–	44
B & C	5	49	10	8	–	–	67
	4	5	27	8	–	–	40
	3	1	2	22	–	–	25
	2	–	–	–	–	–	–
	1	–	–	–	–	–	–
	Total	55	39	38	–	–	132

TABLE IX

Pooled (groups A, B and C) grouping of severity of side effects according to arrangement described in the text.

Second administration	First administration: Nil 5	Slight 4 & 3	Severe 2 & 1	Total
Nil	65	19	0	84
Slight	7	79	4	90
Severe	0	0	2	2
Total	72	98	6	176

The repeated administration of the same analgesic on two occasions to the same patient necessitated a low toxicity on the first occasions. This is shown in table VIII, with the data from all groups pooled together in table IX. Excluding the six cases which had severe toxic reactions (Group A) after the first administration, the similarity between the two successive observations is high ($P<0.001$; $\chi^2=97.22$; $df=2$). A greater number of patients had complete absence of side effects at the second administration, as compared with the first, but the difference is not highly significant ($0.10>P>0.05$; $\chi^2=3.4$; $df=1$). This observation is almost certainly due to the tolerance which is rapidly acquired to the soporific effects of analgesics by some patients.

A summary of the reproducibility of various scores is given in table X. This gives the percentage of instances in which the same score was recorded after two separate administrations of the same drug. This is surprisingly good considering the method depends on the opinion of the patient as the sole criterion for assessment of the efficacy of a drug.

TABLE X

Percentage of patients in whom the second observation was in agreement with the first observation.

Degree of analgesia	Percentage reproducibility: Group A	B	C	B+C	A+B+C
Good (5 & 4)	94	80	90	87	88
Moderate (3)	87	50	50	50	67
Poor (2 & 1)	91	65	80	74	80
Total	90	68	81	77	80
Side effects					
Nil (5)	94	90	88	89	90
Slight (4 & 3)	95	78	74	77	80
Total	86*	83	81	82	82

* This includes 6 cases with severe side effects at the first administration which was not analyzed separately because of the small numbers in this group and the absence of this manifestation in groups B and C.

OTHER APPLICATIONS

While this method of assessing pain relief with different analgesics was designed primarily for use with ambulant out-patients, it can easily be adapted for use in ward patients. Here the drugs will probably not be given with the same regularity as when taken personally by the patient.

TABLE XI

Comparison of scores with dihydrocodeine 30 mg and pethidine 100 mg.

		DIHYDROCODEINE 30 mg												
		Analgesic score						Lack of toxicity						
PETHIDINE 100 mg		5	4	3	2	1	Total		5	4	3	2	1	Total
	5	14	7	2	–	–	23	5	20	1	–	–	–	21
	4	2	8	1	–	–	11	4	10	6	1	–	–	17
	3	2	–	2	5	–	9	3	6	–	8	1	–	15
	2	–	1	3	1	3	8	2	3	–	2	–	–	5
	1	–	–	4	–	7	11	1	–	–	4	–	–	4
	Total	18	16	12	6	10	62	Total	39	7	15	1	–	62

There seems to be less co-operation in regard to completing records with in-patients and this is best overcome by a personal interrogation of the patients at daily intervals. The frequency of administration and dosage of analgesics can be altered more frequently if desired. However, it has been the experience of the author that self-administration at home provided more reliable and reproducible information than in hospitalized cases.

DISCUSSION

The indiscriminate use of this method for the comparison of various analgesic drugs will undoubtedly give erroneous results. Likewise, it must not be credited with giving more information than is intended; for example, one drug can be shown to be less potent (or less toxic) than another, but the degree of difference cannot be accurately assessed. The only means one has to overcome this limitation is to vary the dosages of the drugs concerned until approximately equipotent or equitoxic doses are discovered. Provided one is prepared to expect between 25 and 40 per cent "wastage" of cases for the reasons already given, the method will prove most valuable in answering some of the problems associated with oral analgesics in ambulant patients.

Long-term toxicity cannot be assessed by the method described and it is of little value in comparing the rapidity of onset of tolerance to different drugs. A good example of its limitations for long-term evaluation is given in the appendix. The study there described failed to reveal the severe constipating effect of dihydrocodeine, which has, on occasions, proved of such severity as to terminate its use.

One is impressed with the use of stencilled instruction sheets to patients asking them routinely to record their pain relief, irrespective of whether a drug trial is being carried out or not. This helps enormously in the management of out-patients, as it enables one to see the results of a whole week's treatment and not to be entirely dependent on verbal reports which frequently are coloured by events in the last few days before the interview.

ACKNOWLEDGMENTS

I am indebted to the numerous people who have co-operated in the evolution of this method and in the subsequent studies, particularly to Professor T. C. Gray, Drs. J. E. Riding, A. G. Mackinnon and R. King, and to Mr. J. C. Kilpatrick for his advice on the statistics.

APPENDIX

The following example of the method described is appended to illustrate some of the difficulties encountered.

Comparison of Efficacy of Dihydrocodeine (DHC) 30 mg and Pethidine (P) 100 mg

Identical tablets of these drugs and an inert placebo were prepared by Duncan Flockhart & Co. Cases included were limited to patients with malignant disease.

Total number of cases given both drugs	84
Number of results available for analysis	62
"Wasted" cases	22

These 22 cases consisted of 17 patients who, for one reason or another, were unable to complete the records, or in whom the severity of the pain altered significantly over the period of the trial. The other 5 patients had been on D.D.A. analgesics before this study was started and found that DHC caused marked upset, suggestive of withdrawal symptoms. None of these patients found that these disturbances occurred with pethidine. The subsequent use of placebos and/or tablets containing a mixture of levorphanol and levallorphan confirmed that 4 of these patients were drug addicts. Thus it was shown that DHC is a drug which is not capable of replacing D.D.A. analgesics in addicts and a long-term study confirmed that it has a low addiction potential.

The distribution of scores for analgesia and lack of toxicity are shown in table XI. It was not possible to analyze any of these tables by the "5 × 5, χ^2" technique. By grouping of scores and a direct comparison of the distribution of various grades with both drugs, the following results were obtained.

Analgesia.

The difference between the number of patients having good (5, 4), moderate (3) and no effective (2, 1) pain relief with the two drugs was not significantly different ($0.80>P>0.70$; $\chi^2=0.68$; $df=2$).

Toxicity.

The number of patients who had no side effects (score 5) was significantly greater with DHC than with P ($P<0.001$; $\chi^2=15.05$; $df=1$). There was a significant difference between the incidence of no side effects (5), side effects of moderate severity (4 and 3), and severe side effects (2 and 1) with the two drugs ($P<0.001$; $\chi^2=13.86$; $df=2$).

These show that DHC 30 mg and P 100 mg are approximately equally effective as oral analgesics, but DHC 30 mg produces less severe toxic effects.

Analgesic efficacy.

With the formula already described 11 cases obtained no effective relief with DHC and 19 no effective relief with P. This difference is not significantly different ($0.10>P>0.05$; $\chi^2=2.81$; $df=1$). Calculations of E showed:

DHC 30 mg $E=12.13\pm0.34$
P 100 mg $E=7.90\pm0.77$
($P<0.001$; $t=5.0$; $df=122$)

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THE ANTISIALOGOGUE EFFECT OF PHENOTHIAZINE DERIVATIVES

Comparison of Pecazine, Perphenazine, Fluphenazine, Thiopropazate, Pipamazine and Trifluprομazine

BY

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IT was observed in clinical use that chlorpromazine had some antisialogogue activity (Dobkin, Lamoureux and Gilbert, 1954). In a previous report, specific data were obtained on the saliva suppressing effect of chlorpromazine and promethazine, and the latter was found to be more than 90 per cent effective in the usual dose used for premedication (Dobkin, Wyant and Aasheim, 1958). The present study was undertaken to determine whether several other phenothiazine derivatives, which have satisfactory anti-emetic and sedative properties, might also have significant antisialogogue activity. Such activity would add to their efficacy as pre-anaesthetic medicaments (Dobkin, 1958).

METHOD

Serial tests were done on six healthy adult subjects using a technique that was previously reported (Wyant and Dobkin, 1957). Duplicate tests were done at least 24 hours apart with carbaminoylcholine chloride-adrenaline mixture (control), pecazine (Pacatal), perphenazine (Trilafon, Fentazin), fluphenazine (Trancin), thiopropazate (Dartal), pipamazine (Mornidine), and trifluпromazine (Vesprin). Each subject had at least fourteen tests. The intravenous dose of each drug was selected after preliminary tests to determine that dose which produced no subjective or objective effect except moderate drowsiness and a dry sensation in the mouth.

In the control test, saliva was collected for 10 minutes before any drug was administered and then for 30 minutes after the intravenous injection of a mixture containing carbaminoylcholine chloride and adrenaline. In the comparative tests, each drug was injected intravenously at the beginning of the experiment, and saliva was collected for 10 minutes. Then the mixture of carbaminoylcholine chloride-adrenaline was injected and saliva was collected for a further 30 minutes. The same parotid duct which was initially selected in each subject was used throughout the series, and the volumes collected were recorded at 10-minute intervals.

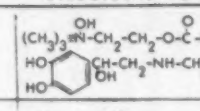
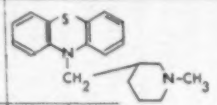
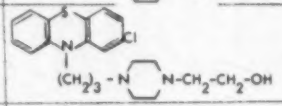
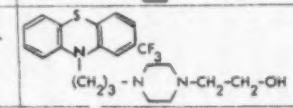
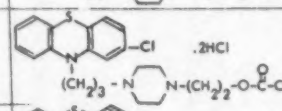
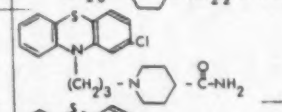
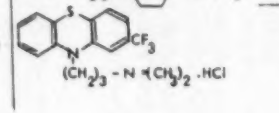
RESULTS AND DISCUSSION

A summary of the data is shown in the table. The mean volume of saliva collected during the 10 minutes immediately following the injection of the mixture of carbaminoylcholine chloride-adrenaline was taken as 100 per cent. All other volumes of saliva that were collected were then computed on this percentage basis. Standard deviations were calculated from the mean volumes of salivary secretion, expressed as a percentage as noted above, with each drug, at each time interval.

Pecazine and perphenazine caused marked suppression of salivary secretion during the initial 10-minute period, but were only about 30 per cent effective in preventing the stimulant action of the carbaminoylcholine chloride-adrenaline. One subject was very drowsy after the tests with perphenazine.

The other four drugs caused only slight suppression of saliva during the initial 10-minute period, but were more effective in suppressing the stimulant effect of the stimulant mixture. Thiopropazate and pipamazine were about 60 per cent effective, whereas trifluпromazine and fluphenazine were somewhat less effective.

Three of the subjects were very drowsy after the tests with fluphenazine, thiopropazate and pipamazine. Thiopropazate, pipamazine and trifluпromazine caused slight pain during injec-

DRUGS	OFFICIAL & CHEMICAL NAME	STRUCTURAL FORMULA	INTRAVENOUS DOSE mg.	SECRETION OF SALIVA % OF CONTROL TEST RESPONSE WITH CARBACHOL - ADRENALINE 10min BEFORE	10min. AFTER	20min. AFTER	30min. AFTER	% REDUCTION OF SALIVARY SECRETION
CARBACHOL ADRENALINE (CONTROL)	**Carbaminoylcholine** **Adrenaline**		0.12 0.06	7 12	100 54	4 4	1 1	-
PACATAL	**Pecazine (Warner Chilcott)** **10-(N-methyl-3-piperidylmethyl) phenothiazine acetate**		10	2 0.3	67 48	8 4	5 7	33
TRILAFON	Perphenazine (Schering) 1-(2-hydroxyethyl)-4-[3-(2-chloro-10-phenothiazi-propyl] piperazine		5	0.3 0.7	65 55	7 10	2 3	35
TRANCIN	Fluphenazine (Schering) 1-(2-hydroxyethyl)-4-[3-(2-trifluoromethyl-10-phenothiazi-propyl] piperazine		1	4 3	60 50	6 6	2 3	40
DARTAL	Thiopropazate(Searle) 1-(2-acetoxyethyl)-4-[3-(2-chloro-10-phenothiazi-propyl] piperazine dihydrochloride		2.5	5 11	35 21	2 4	6 12	65
MORNIDINE	Pipamazine (Searle) 10-[3-(4-carbamoylpiperidino)propyl] -2 chlorphenothiazine		2.5	9 12	40 48	6 9	2 5	60
VESPRIN	Triflupromazine (Squibb) 10-(3-dimethylaminopropyl)-2-(trifluoromethyl) phenothiazine hydrochloride		5	3 5	51 33	6 17	3 4	49

tion even when greatly diluted. One subject developed phlebitis following the injections of both thiopropazate and pipamazine.

SUMMARY AND CONCLUSIONS

The effect of salivary secretion of intravenous pecazine, perphenazine, fluphenazine, thiopropazate, pipamazine and triflupromazine was compared in six healthy adult subjects. A mixture of carbaminoylcholine chloride and adrenaline was injected to stimulate secretions. The dose selected for each drug was that which produced no undesirable effects except drowsiness. Thiopropazate was the most effective antisialogogue in this group. Pipamazine and triflupromazine were less effective. Pecazine, perphenazine and fluphenazine were weak antisialogogues. Therefore, whenever these three drugs are used for pre-anaesthetic medication it is advisable to combine them with a therapeutic dose of either scopolamine or atropine.

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CORRESPONDENCE

THE PROPERTIES OF 1:1:2-TRIFLUORO-1:2-DICHLOROETHANE

Sir,—I was very interested to read, in the December 1959 issue of your journal, the article by Burn, Epstein and Goodford (*Brit. J. Anaesth.*, **31**, 518) on the properties of 1:1:2-trifluoro-1:2-dichloroethane. I and my colleagues examined this compound some time ago as part of our work on general anaesthetics carried out in collaboration with Dr. C. W. Suckling of the General Chemicals Division of I.C.I. Ltd. We rejected it as a potential candidate for clinical trial in humans: we had found just the same cardiac arrythmias and were reluctant to proceed any further with a compound having these properties.

In general our results were similar to those described by Burn and his collaborators, but some additional findings by us may be worth recording. They are as follows:

(1) In mice we found the anaesthetic concentration (AC 50) to be 3.1 per cent v/v, and the lethal concentration (LC 50) 9.2 per cent v/v, giving a therapeutic ratio LC 50/AC 50 of about 3, which is about twice that of ether (1.7) and slightly smaller than that of halothane (3.3).

(2) Cats, rabbits, and dogs, especially when unpremedicated, required higher concentrations than those producing anaesthesia in mice. In cats the safety margin was rather small; they were anaesthetized when they inhaled the compound in relatively high concentrations, but were killed with mixtures that produced only slight anaesthesia.

(3) The hypotension produced in these animals by anaesthetic concentrations was more intense than that caused by iso-narcotic concentrations of halothane.

(4) E.c.g. irregularities were not observed in dogs, but were recorded in both rabbits and in cats. However, they were atropine-resistant in the cat but were abolished by this drug in the rabbit, and probably had different origins in the two species.

(5) Like some other anaesthetics the compound sensitized the heart to adrenaline. This hypersensitivity was not very different in intensity from that produced by halothane.

(6) The compound produced congestion and oedema of the lungs even when administered in concentrations that produced only light anaesthesia. The histological examination of these lungs suggested that the intensity of the lesions was proportional to the concentration of the inhaled mixture.

(7) The compound was somewhat unstable when recirculated over moist soda lime kept at 60°C; these conditions are similar to those found in closed-circuit anaesthesia.

J. RAVENTÓS

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Brit. J. Anaesth. (1960), 32, 60

TEMPERATURE CHANGES IN CHILDREN DURING GENERAL ANAESTHESIA

BY

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THE state of anaesthesia depresses and renders inefficient the temperature regulating mechanisms of the body. Placed in conditions of high ambient temperature with which its deranged compensatory mechanisms cannot adequately cope, the body temperature of the anaesthetized patient has been shown to rise. This is especially so in children in whom there are the additional factors of small body mass, high internal heat production and immature heat regulatory mechanisms. The foregoing and the evil effects of hyperpyrexia in the anaesthetic state—notably convulsions and death—are well documented (Knight, 1942; Bigler and McQuiston, 1951; Searles and Lenahan, 1952; Clarke, Orkin and Rovenstine, 1954).

The air-conditioning of operating theatres, as originally recommended by Huntington in 1920 (Searles and Lenahan, 1952), is a logical solution to the problem of heat accumulation during anaesthesia and is now widely accepted in the normal design of operating theatres. There are, however, no published observations on the body temperatures of subjects anaesthetized in such surroundings.

The advent of halothane which appears to cause a more profound disturbance of the body heat regulatory mechanism than does ether, the agent most commonly used in the papers referred to, provided a further stimulus to this study.

We report here on a statistical analysis of observations of body temperature made on 248 infants and children undergoing general anaesthesia and surgery. The rectal temperature, which was recorded with a low reading mercury thermometer, was taken as the most reliable indication of body temperature (Machle and Hatch, 1947) and is used exclusively in this study.

CONDITIONS AND METHODS

The operating theatre.

The operating theatre in which these observations were made is air-conditioned. Air is passed into the theatre from central overhead louvres at a rate of 900 cubic feet per minute, passing out through louvres in the wall of the theatre. Humidity is controlled by "dewpoint" control. The conditioning was set at 75°F with relative humidity of 75 per cent. The actual theatre temperature was recorded in every case with a mercury dry bulb thermometer fixed to the theatre wall. Relative humidity was calculated from this and that recorded by a mercury wet bulb thermometer. The actual temperature and humidity did not vary widely from the limits of setting of the air condition automatic control. Observations extended over both winter and summer.

The drapes.

The standard draping of patients for operations was as follows:

Lower part of body	1 macintosh, 1 sheet.
Chest and arm	2 sheets.
Neonates:	In addition to the above, neonates were insulated with rolls of cotton wool placed along their sides.

The observations made.

The following observations were made on each patient:

Weight and length:

From these the *surface area* was calculated, using the tables of Du Bois and Hannon (Du Bois, 1936).

Age.

Pre-operative and postoperative temperatures: From these the change in temperature was calculated.
Nature of the operation.
Duration of operation and anaesthesia.
Volume of blood replaced.

Anaesthesia.

(1) Halothane group: 166 cases were anaesthetized with halothane, nitrous oxide and oxygen.
(2) Miscellaneous group: 82 cases were anaesthetized with nitrous oxide and oxygen and ether and/or cyclopropane or trichloroethylene. Of these the majority were given ether. In this group 17 cases had anaesthesia induced with halothane, administered for up to 5 minutes.

The agents were administered by means of a modified T-piece system with mask or endotracheal tube, utilizing a high flow of fresh gases, 6 litres per minute. For thoracic and abdominal operations an I.P.P.R. technique was used; the adjuvant use of relaxant drugs, though necessary in the miscellaneous group, was seldom necessary in the halothane group. Thiopentone sodium was used for induction of anaesthesia in very few cases.

Premedication.

All cases with the exception of half of those in the miscellaneous group, who were given scopolamine, were given atropine sulphate on a dose/weight basis. In addition to this some of the patients were given pethidine or papaveretum also on a dose/weight basis.

RESULTS

The observations of change in the body temperature were submitted to statistical analysis in relation to the various factors recorded that would influence the body temperature. The results of such analysis are submitted as histograms.

General results.

The range of age in our cases was from premature newborn to 11 years. The weight range in these cases was from 3 lb. 12 oz. to 96 lb. The range of duration of anaesthesia was from 20 minutes to 360 minutes.

Temperature.

There was a mean fall of temperature in all cases as follows (see figure 1 and table I).

Halothane group: Mean fall 2.1°F (range: −8.4°F to +2°F).

Miscellaneous group: Mean fall 1°F (range: −10°F. to +3°F).

The difference is statistically highly significant.

Detailed Analysis of Temperature Change with Relation to Various Influential Factors.

Theatre temperature.

The theatre temperature and humidity are the most important factors in causing a rise or fall of the temperature of the anaesthetized patient. We stress again that our theatre was air-conditioned and, though the temperature recorded ranged from 63°F to 81°F, the temperature in the majority of cases was between 71°F and 75°F. This is well within the range of ambient

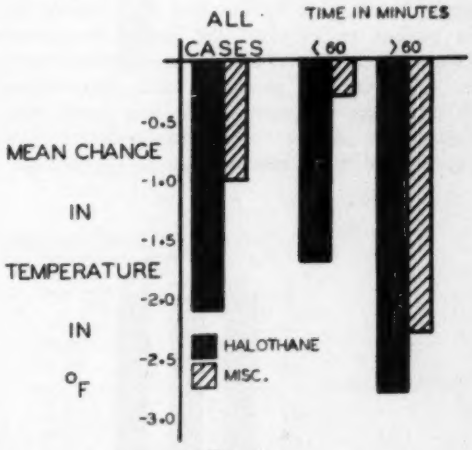

FIG. 1
General histogram.
Mean fall in body temperature in 166 patients anaesthetized with halothane, compared with 82 patients anaesthetized by other methods.

TABLE I (A)

Anaesthetic	Mean change in temp. degrees Fah.	S.D.	S.E.	Number of cases
Halothane	−2·1	1·90	0·15	166
Miscellaneous	−1·1	2·58	0·28	82

TABLE I (B)

Time in minutes	Mean change in temp. degrees Fah.		S.D.		S.E.		Number of cases	
	Halothane	Misc.	Halothane	Misc.	Halothane	Misc.	Halothane	Misc.
<60	−1·7	−0·3	1·58	1·34	0·15	0·18	107	53
>60	−2·8	−2·3	2·30	3·65	0·30	0·68	59	29

temperature at which loss of heat by radiation is highly efficient—i.e. loss of heat by evaporation is of less importance to the body, and is well below the temperatures recorded by other observers at which heat accumulation with all its unpleasant sequelae occurs (Knight, 1942; Bigler and McQuiston, 1951; Searles and Lenahan, 1952; Clarke et al., 1954). The results of an analysis of temperature change in the patient in relation to theatre temperature are reflected in figure 2 and table II. There is an increased fall in patient temperature the lower the theatre temperature. The differences are significant only in the halothane group in our observations. A histogram is submitted for this group only. Calculation of the correlation coefficient (0.4) revealed no linear relationship.

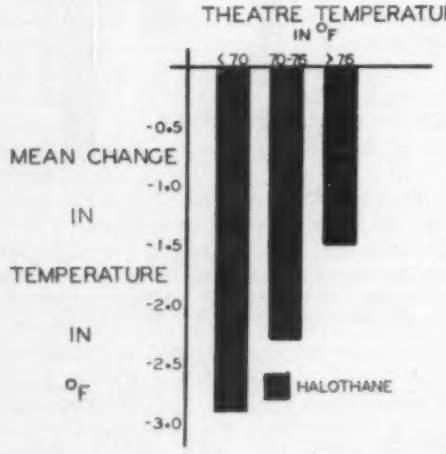

FIG. 2
Mean change in temperature with relation to theatre temperature.

TABLE II

Theatre temp. degrees Fah.	Mean change in temp. degrees Fah.	S.D.	S.E.	Number of cases
<70	−2·9	2·10	0·51	17
71—75	−2·3	1·87	0·19	96
>76	−1·5	1·89	0·26	53

Humidity.

Because of the air conditioning, the range of humidity recorded in this series was relatively narrow, 65–87 per cent, with the majority falling in the range 71–75 per cent. In no case was the actual wet bulb temperature above 75°F, the temperature stressed by Clarke et al. (1954) above which they most consistently observed heat accumulation. Bearing in mind the theatre temperatures recorded in our cases it is hardly surprising that analysis of our cases revealed no relation between the temperature change in the patient and the relative humidity.

Duration of anaesthesia.

Analysis of temperature change in the patient in relation to duration of anaesthesia is illustrated in figures 1 and 3 and tables I and III. There is an increasing fall in temperature with the passage of time. This correlation is not linear, correlation coefficient −0.4. With halothane especially there is a rapid initial drop in temperature whereupon the temperature achieves a plateau level, there being no statistical difference between the mean temperature change in the three arbitrary time groups up to 120 minutes. In operations extending beyond 120 minutes a further significant drop in temperature is evident. This latter group, however, consists largely of "smaller" babies to which reference is made in the sections following. The difference in fall in temperature between the halothane

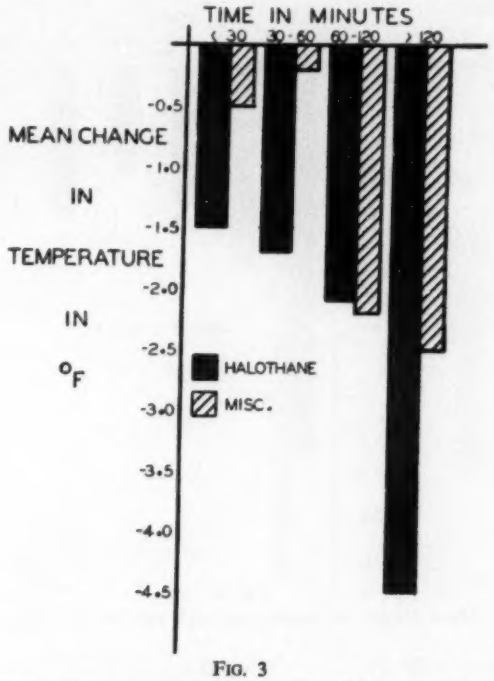

FIG. 3
Mean change in temperature with relation to time.

TABLE III

Time in minutes	Mean change in temp. degrees Fah.		S.D.		S.E.		Number of cases	
	Halothane	Misc.	Halothane	Misc.	Halothane	Misc.	Halothane	Misc.
<30	−1·5	−0·5	1·5	1·66	0·27	0·5	32	11
30−60	−1·7	−0·2	1·6	1·29	0·18	0·20	75	42
60−120	−2·1	−2·2	1·7	1·53	0·26	1·8	41	23
>120	−4·5	−2·5	2·7	4·2	0·64	0·28	18	6

group and that of the miscellaneous group is significant only for the period up to 60 minutes.

Weight.

Analysis of the change in temperature with relation to the weight of the patients (fig. 4 and table IV) reveals that there is a significantly greater fall in temperature in the infants and children who weigh less than 20 lb. than in those who exceed this weight. Whereas with these latter, the fall in temperature is significantly greater with halothane than in the miscellaneous group, there is no significant difference in the fall in temperature between the two groups in the infants who weigh less than 20 lb. Calculation of the correlation coefficient (0.4) reveals no linear relationship between fall in temperature and weight.

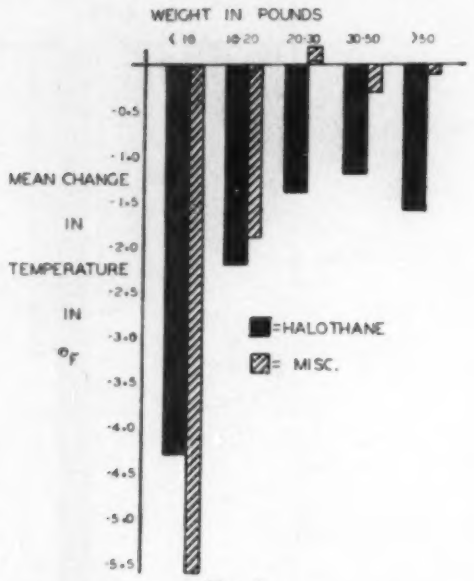

FIG. 4
Mean change in temperature with relation to weight.

TABLE IV

Weight in lbs.	Mean change in temp. degrees Fah.		S.D.		S.E.		Number of cases	
	Halothane	Misc.	Halothane	Misc.	Halothane	Misc.	Halothane	Misc.
<10	−4·3	−5·6	2·19	3·18	0·39	1·13	32	8
10−20	−2·2	−1·9	1·72	3·50	0·30	1·05	32	11
20−30	−1·4	+0·2	1·50	2·27	0·25	0·58	38	15
30−50	−1·2	−0·3	1·28	1·17	0·20	0·21	42	29
>50	−1·6	−0·1	0·81	1·12	0·17	0·25	22	19

Surface area.

The greater cooling of the smaller infants is again borne out by calculation of the mean fall in temperature in relation to surface area (see fig. 5 and table V). In this case the infants with a surface area of less than 0.3 sq.m cool to a significantly greater extent than those with a larger surface area. Again, in these latter, a plateau effect is evident. This lack of linear correlation is confirmed by a correlation coefficient of 0.4.

As it is thought that the degree of temperature change is influenced more by the ratio the mass of the child bears to its surface area than to these two factors separately, the cases were analyzed for temperature change in relation to the ratio surface area/weight. This analysis, however, revealed nothing not apparent in the foregoing analysis and is consequently not submitted.

Duration of anaesthesia and weight of infant.

The relation of the temperature change to the duration of the anaesthetic and to the size of the infant elicited in the foregoing analyses is further amplified when the observations of change in

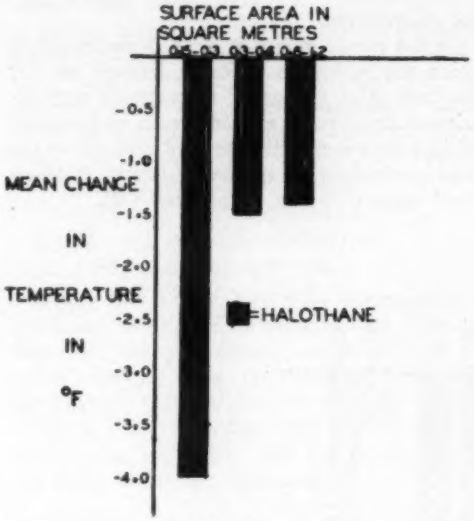

FIG. 5
Mean change in temperature with relation to surface area.

TABLE V

Surface area in sq. metres	Mean change in temp. degrees Fah.	S.D.	S.E.	Number of cases
0·15—0·3	−4·0	2·09	0·32	43
0·3 —0·6	−1·5	1·60	0·22	54
0·6 —1·2	−1·4	1·14	0·16	69

temperature are broken down to reflect both these factors simultaneously (see fig. 6 and table VI). In this analysis the cases are divided as follows:

(1) Children weighing less than 20 lb.
(2) Children weighing more than 20 lb.

These groups are then subdivided on the basis of the duration of anaesthesia: (*a*) anaesthesia of a duration less than 60 minutes; (*b*) anaesthesia of a duration longer than 60 minutes. It is

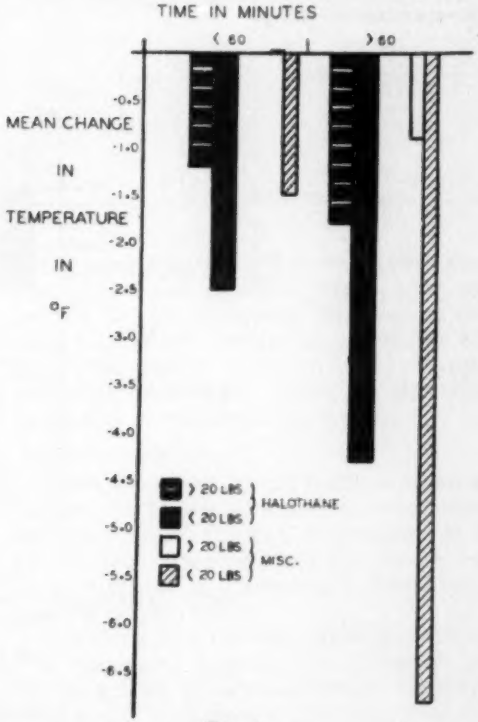

FIG. 6
Mean change in temperature with relation to time and weight.

TABLE VI

Time in minutes		Mean change in temp. degrees Fah.		S.D.		S.E.		Number of cases	
		<20 lbs.	>20 lbs.	<20 lbs.	>20 lbs.	<20 lbs.	>20 lbs.	<20 lbs.	>20 lbs.
<60	Halothane	−2·5	−1·2	1·9	1·30	0·27	0·16	39	68
	Misc.	−1·5	+0·1	1·7	0·98	0·50	0·15	12	42
>60	Halothane	−4·3	−1·8	2·6	1·24	0·49	0·22	28	31
	Misc.	−6·8	−0·9	4·12	2·04	1·60	0·45	7	21

apparent that, regardless of the anaesthetic, not only do the smaller infants have a greater fall in temperature than the larger, but this fall is progressively greater with increased duration of anaesthesia. The use of halothane produces a significantly greater fall in temperature in the larger children than occurs in these children in the miscellaneous group.

Site of operation.

On the site of operation depends the extent to which the patient is exposed. Analysis of our observations of change of temperature with relation to the site of operation reveals an increased fall in temperature with increased exposure of the child particularly of viscera as occurs in abdominal surgery (see fig. 7 and table VII).

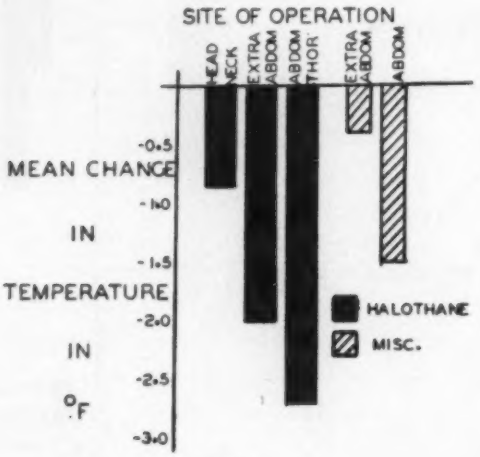

FIG. 7
Mean change in temperature with relation to site of operation.

TABLE VII

	Site of operation	Mean change in temp. degrees Fah.	S.D.	S.E.	Number of cases
HALOTHANE	Head and neck	−0·8	1·13	0·18	38
	Extra abdominal	−2·0	1·17	0·18	42
	Thoracic and abdominal	−2·7	1·97	0·21	85
MISC	Extra abdominal	−0·4	2·29	0·37	38
	Abdominal	−1·5	2·69	0·40	44

Pre-operative temperature.

Bearing in mind the possible part pre-operative pyrexia plays in the production of hyperthermia and "ether convulsions" we analyzed our observations of change in temperature during operation in relation to the patient's pre-operative temperature. This latter we arbitrarily divided into three groups as follows:

(1) Less than 98°F—hypothermic.
(2) 98° and 99°F—normothermic.
(3) 100°F and over—pyrexial.

Figure 8 and table VIII show that, under the conditions of theatre temperature and humidity described, the pre-operative temperature of the patient had no effect on the mean change in temperature which was nevertheless a fall. (Though there is a difference of 1°F between the hypothermic group and the others, this is not quite statistically significant.)

Blood replacement.

The transfusion into the patient of cold blood can be expected to lower the patient's body temperature. Analysis of our cases on this basis confirms this (see fig. 9 and table IX). The mean fall in temperature is 1.6°F greater in those cases that had a blood transfusion than in those that did not. It must be pointed out, however, that those patients who received blood were, by and large, the smaller babies having prolonged operations—two factors which of themselves cause a fall in temperature in our cases.

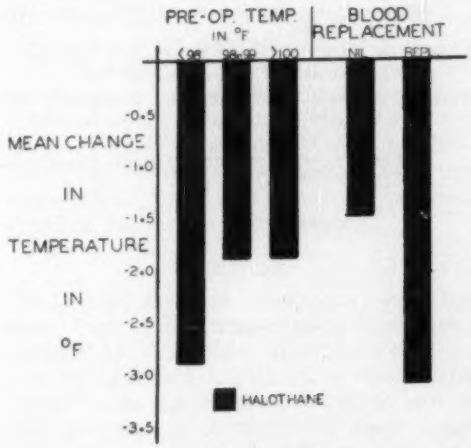

FIG. 8
Mean change in temperature with relation to pre-operative temperature.

FIG. 9
Mean change in temperature with relation to blood replacement.

TABLE VIII

Pre-operation temp. degrees Fah.	Mean change in temp. degrees Fah.	S.D.	S.E.	Number of cases
<98	−2·9	2·78	0·50	31
98 & 99	−1·9	1·76	0·17	103
>100	−1·9	1·13	0·20	32

TABLE IX

Blood replacement				
Nil	−1·5	1·70	0·17	105
Blood replaced	−3·1	2·18	0·29	56

Neonates.

In this series there were 16 neonates. All except one were anaesthetized with halothane, nitrous oxide and oxygen. Duration of anaesthesia in 11 of these cases was longer than 120 minutes, and in the remaining 5 duration of anaesthesia was from 60 to 120 minutes.

In addition to the standard draping described, 5 of these little patients were placed on the operating table on hot-water bottles containing water at 101°F. Whereas in the 11 not so treated the mean fall in temperature was 5.9°F (S.D. 2.3, S.E. 0.69), that in the 5 placed on hot-water bottles was 3.2°F (S.D. 2.9, S.E. 1.6). The mean end anaesthetic temperature of the two groups was 89.6°F and 93.5°F respectively. We are of the opinion that though some fall in temperature is in all probability beneficial during anaesthesia, neonatal temperatures ought to be monitored as the fall is often precipitous and falls of 6°F to 8°F are not uncommon. The temperature should not be permitted to fall below 90°F. One of our cases in whom the temperature dropped to 84°F developed hypothermic apnoea, respiration only being resumed on warming. A further danger

of extreme falls in temperature is the possible onset of sclerema (Rees, 1958).

SUMMARY

We report here on a statistical analysis of observations of body temperature made on 248 infants and children undergoing general anaesthesia and surgery. These observations were made in an air-conditioned operating theatre.

There was a mean fall in temperature during general anaesthesia. This was 2.1°F in the group of cases anaesthetized with halothane and 1°F in a group anaesthetized with other anaesthetics.

The benefit of the air conditioning of the operating theatre is stressed. Over the observed range of theatre temperatures there was a positive relation between this and the patient's change in temperature. In this range of theatre temperature the comparatively narrow range of relative humidity observed had no bearing on the change in temperature of the patient.

Small infants (less than 20 lb.) cool to a significantly greater extent than the larger and this fall is progressive with time. The larger infants (more than 20 lb.) after an initial rapid fall in temperature (especially with the use of halothane), attain a relatively static temperature. Similar conclusions follow an analysis of the fall in temperature in relation to the patient's surface area.

The fall in temperature is related to the site of operation: the greater the exposure, especially of viscera, the greater the fall in temperature.

The presence of pyrexia before operation had no bearing on the change in temperature during anaesthesia.

The transfusion of blood led to an increased fall in temperature.

The mean fall in temperature in neonates was 5.9°F. When hot-water bottles at 101°F were placed under the patient, the mean fall was 3.2°F.

ACKNOWLEDGMENTS

We wish to express our gratitude to Drs. Weinreich and Malherbe who collected much of the data, and to Professor Pollard of the University of Cape Town for statistical advice. We also thank Dr. J. Mostert, Superintendent of the Red Cross War Memorial Children's Hospital, for permission to publish these observations, and Professor J. H. Louw and the surgical staff for their patience and co-operation.

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Brit. J. Anaesth. (1960), **32**, 69

ANAESTHESIA FOR CARDIAC CATHETERIZATION IN CHILDREN

BY

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CARDIAC surgery owes much of its present success to the fact that the anatomy and functional consequences of the abnormality can be demonstrated pre-operatively in a high proportion of cases. To this end, however, clinical examination of the patient must be supplemented by special investigations such as cardiac catheterization and angiocardiography. These investigations are prolonged and unpleasant for the patient and, since they must often be carried out on children, sedation or anaesthesia is required. Anaesthesia for angiocardiography presents no special difficulty but the preparation of children for cardiac catheterization has given rise to much speculation and dispute. The problem is generally agreed: the patient must be at rest for a prolonged period; there must be no significant disturbance of haemodynamics and no interference with the analysis of blood gases. These conditions must be provided in the complete darkness of an X-ray room, in patients who may be very poor risks. In this paper a brief historical review will be presented of the attempts that have been made to meet these requirements. Following this a description will be given of a small series of cases anaesthetized by a technique not previously described for cardiac catheterization.

HISTORY

The whole literature concerning anaesthetic methods for cardiac catheterization in children is coloured by the general assumption than any form of inhalation anaesthesia is unacceptable. Nitrous oxide and ether are known to interfere with blood gas analysis by the Van Slyke method but, quite apart from this difficulty, any anaesthetic technique involving the administration of more or less than the atmospheric concentration of oxygen will result in alterations of blood oxygen saturation. For these reasons, inhalation anaesthesia came to be ruled out and numerous alternative expedients were devised, some of which are still in common use.

Most of the earlier papers described methods involving heavy sedation, usually by the rectal route. Holling and Zak (1950), having found that both trichloroethylene and paraldehyde interfere with blood gas analysis, used avertin supplemented with thiopentone. They recognized that this technique probably altered the physiological state of the patient, but they rightly felt that it did so less than crying and struggling. J. A. Smith (1950) suggested rectal thiopentone supplemented with the same agent intravenously. Light, Livingstone and Adams (1950) found rectal avertin satisfactory as the sole agent but reported only 16 cases. Lee (1950) suggested premedication with atropine and pentobarbitone, followed by intravenous thiopentone, local infiltration, and subsequent injection of thiopentone through the cardiac catheter. Inglis (1954) found that if rectal thiopentone was followed by pethidine instead of intravenous thiopentone, narcosis was less prolonged. Fieldman et al. (1950) also noted slow recovery, and remarked on the 4–5 per cent fall in arterial oxygen saturation which resulted from supplementary injections of thiopentone.

Kepes, Livingston and Escher (1955) reviewed the disadvantages of heavy sedation and observed that even small doses of drugs given by rectum occasionally disturb circulatory compensation: they illustrated this with a case report. Their desire to provide a steady physiological state led them to prefer general anaesthesia with nitrous oxide and oxygen, although they admitted that this may cause some alteration of blood oxygen saturation. Despite their misgivings about the circulatory effects of rectal sedation, the authors seemed happy to supplement their anaesthesia with intravenous thiopentone when necessary. The problems of the darkened X-ray room, the explosion

danger and the hazards of radiation were referred to. The paper is also one of the few which mention the importance of measuring and replacing lost blood.

An interesting technique was described by Keown, Fisher, Downing and Hitchcock (1957) using avertin, followed by intramuscular thiopentone with hyaluronidase. Unfortunately few details were supplied although the series comprised 1,018 cases. Respiratory depression was the most significant complication.

In recent years the use of "tranquillizing agents" has become widespread and it was inevitable that their merits should be exploited in the management of children undergoing cardiac catheterization. The usual combination has been pethidine, chlorpromazine and promethazine, and varying degrees of success have been claimed. Mitchell and Minor (1958) found the mixture safe, easy to use and effective. They believed that it reduced postoperative complications and minimized the need for nursing care. In a total of 89 patients, they had 3 instances of hypotension and 6 of tachycardia. C. Smith, Rowe and Vlad (1958), using a similar combination of drugs, admitted one death in 670 cases. Many of the children required supplementary sedation and 2.7 per cent still remained restless and were regarded as failures. Lundy (1958, 1959) uses rectal thiopentone followed by methorphinan and levallorphan, phenergan and alphaprodine (NNR), and local infiltration for venostomy. Finally, bemegride and amiphenizole are given, with oxygen and vasopressors if necessary. This technique, when last reported, had been used in 133 cases and was claimed to be satisfactory, although it was admitted that some children are difficult to manage. Three cases of hypotensive death had occurred. The detailed instructions to be followed, and the multiplicity of drugs, make the method time-consuming and exacting.

Keats, Telford, Kurosu and Latson (1958) expressed dissatisfaction with all the above techniques, pointing out that the data obtained are difficult to interpret if the level of anaesthesia and degree of oxygenation are uneven. They found that a steady state could be obtained with trichloroethylene in air following heavy sedation and at the time of their publication they had used this method in 225 cases. The importance of a clear airway was stressed, all patients under 2 years of age, and many others, being intubated. They found that the method did not appreciably interfere with blood gas analysis, even by manometric methods. It was admitted that induction was slow and that there was a tendency to tachypnoea, tachycardia and arrhythmia; they felt, however, that if a more satisfactory non-flammable agent were available, the method would approach the ideal. Their paper is important because it describes a return to the use of general inhalation anaesthesia for cardiac catheterization in children. It is the first published account of the administration of a volatile agent in air for this procedure.

PERSONAL EXPERIENCES

In the Nuffield Department of Surgery, the first children presenting for cardiac catheterization were managed by methods derived from the literature, but these gave only moderate satisfaction. The first 30 cases were premedicated with pethidine and phenothiazine derivatives, administered on a weight basis. The mixture used contained pethidine, promethazine and chlorpromazine in the proportions of 4:1:1 and this mixture was administered, intramuscularly, on the basis of 25 mg of pethidine per 20 lb. body weight. These doses were reduced by one-third for cyanosed patients. This premedication was supplemented as required, either with small intravenous or intramuscular doses of the same mixture, or with intravenous thiopentone. The results were unpredictable and it was not possible to achieve the high degree of success claimed by the Canadian workers who described the use of the mixture (Smith, Rowe and Vlad, 1958). It may be that British children are less sophisticated than their transatlantic contemporaries and more easily frightened by the complex appurtenances of up-to-date hospital investigation. Intravenous use of the mixture was soon abandoned because of the relatively high incidence of tachycardia, which was attributable to the drugs in at least 7 of the 30 cases. Intravenous injections also produced transient falls in arterial pressure and respiratory minute volume, with consequent disturbance of haemodynamics and oxygen saturation.

Case 1. Intravenous pethidine and promethazine gave rise to auricular tachycardia at a rate of over 300 per minute for 5 minutes.

Case 2. Intravenous promethazine and chlorpromazine caused a rise in heart rate from 125 to 160 per minute. The child developed congestive cardiac failure in the postoperative period.

Case 3. In this case intravenous injection of the same drugs caused an immediate rise in pulse rate from 88 to 140 per minute. This tachycardia persisted for 20 minutes.

It was also noted that when repeated doses of these drugs were required, severe postoperative circulatory and respiratory depression sometimes occurred.

Case 4. This 7-year-old child required large doses of drugs to maintain quiescence during catheterization, at the end of which she was pale and hypotensive, with depressed respiration. Nalorphine and respiratory stimulants were required before the child could be returned to the ward. Angiocardiography which had been planned, was postponed on account of her unsatisfactory general condition.

As a result of these experiences a change was made to the use of rectal thiopentone. This was found to produce much more reliable results. However, it rarely lasted long enough and intravenous supplements had the same disadvantages as with the previous medication. In addition, there was a tendency for the anaesthesia to wear off suddenly and for the child to become restless without warning. This sometimes interfered with the catheterization findings.

Case 5. A pulmonary artery oxygen saturation of 72 per cent had been recorded, and a few minutes later the child suddenly woke up and struggled. Fifty milligrams of thiopentone were administered intravenously, and a second sample from the same position then showed and oxygen saturation of 62 per cent. In view of this discrepancy, a third sample from the same site was taken some 10 minutes later and this showed 70 per cent saturation. Such fluctuations could clearly be misleading in the diagnosis of an intracardiac shunt.

PRESENT TECHNIQUE

In addition to the disadvantages already discussed, neither of the above methods could be regarded as satisfactory from the anaesthetist's point of view, since in a dark room, surrounded by apparatus, contact with the patient was much too tenuous. We decided, therefore, to approach the problem afresh.

After consulting our laboratory colleagues, we concluded that none of the conventional objections to inhalation anaesthesia was unsurmountable. We felt that the use of light general anaesthesia, with endotracheal intubation, would provide much greater safety for the patient. We also felt, with other workers, that diagnostic oxygen saturation determinations would be more reliable and consistent during an evenly maintained anaesthesia than during the alternate restlessness and depression which result from other methods. The principal objection was, of course, to the use of oxygen-rich mixtures and anaesthetic gases, but we felt that we could overcome this difficulty by using low concentrations of a volatile agent vaporized in room air.

The agent we selected for anaesthesia was the azeotropic halothane-diethyl ether mixture. Our previous experience with this mixture had convinced us of its safety when used in low concentrations, even for prolonged periods of time and in bad risk patients. The impressively low incidence of cardiac arrhythmias under circumstances when these are particularly liable to arise has previously been noted (Adams, Lambrechts and Parkhouse, 1959). The azeotrope is one agent which fulfills the criteria of Keats, Telford, Kurosu, and Latson (1958), being potent and rapidly eliminated. In clinically used concentrations it is also nonexplosive. We make no claim that it is the only volatile agent suitable for the technique we describe, nor that it possesses any innate superiority; it is merely the agent that we chose to employ.

Our next problem was whether or not to use controlled ventilation. The advantages of controlled ventilation in paediatric anaesthesia are well known (Rees, 1958), but we anticipated some opposition to its use during catheterization on the grounds of possible interference with differential intravascular and intracardiac pressure recordings. However, after some early experiences in which spontaneous respiration was allowed to persist, we came to feel that the advantage of having absolute control over the tidal and minute volume of the patient would more than outweigh any theoretical disadvantage. Furthermore, with complete muscular paralysis a sick child can be spared the effort of breathing and immobility can be ensured at the lightest possible level of anaes-

thesia. Arterial oxygen saturation is not significantly altered during controlled ventilation with air. Hyperventilation will, of course, alter carbon dioxide tension but this is rarely measured during catheterization and in any case, if the patient's minute volume is regulated according to the Radform (1955) nomogram or Nunn's suggested modification (Nunn, 1959), gross departures from normal carbon dioxide tension should not occur.

Intermittent positive pressure ventilation, when properly applied, produces only slight changes in the haemodynamics of the normal subject (Cournand, Motley and Werko, 1947). Figure 2 is a tracing obtained during catheterization of a child without significant cardiac abnormality; it shows simultaneous femoral arterial pressure, tracheal pressure, and right auricular pressure during intermittent positive pressure ventilation. Even in patients with cardiac disease, including those with intracardiac shunts, it is unlikely that gentle passive ventilation of the lungs will cause any significant disturbance, and it is worthy of note, in this connection, that for many years intermittent positive pressure ventilation has been an accepted part of anaesthetic technique during angiocardiography and also during thoracotomy in such patients. It is well known that the child with an intracardiac shunt may become deeply cyanosed during crying or straining but in these circumstances the intrathoracic positive pressure is much higher and much more sustained than during controlled ventilation. The case report below (Case 7) is an example of a child with a ventricular septal defect who was subject to frequent cyanotic attacks during crying. This child received intermittent positive pressure ventilation during catheterization, and again during thoracotomy for the repair of his defect, without any evidence of reversal of his shunt. It has been reported from some centres (Hodgson, 1959) that, in patients with bi-directional shunts and approximately equal left- and right-sided pressures, the institution of controlled ventilation may be sufficient to cause cyanosis and serious deterioration in general condition. This possibility should certainly be borne in mind, although workers in other centres, with an equally large experience of congenital heart disease, have not reported the complication.

METHOD

A standard anaesthetic technique is now employed for all cardiac investigations in children. Premedication is with phenergan 0.5 mg/lb., and pethidine 1 mg/lb., these doses being reduced for patients in very poor physical condition. On arrival in the angiocardiography room, anaesthesia is induced either with the azeotrope or with a small intravenous injection of thiopentone, according to the age and preference of the child. Full muscular relaxation is then obtained either with intravenous gallamine or with intermittent suxamethonium injections. The patient is intubated and his ventilation is controlled throughout the procedure with air containing 0.4–0.6 per cent azeotrope.* Very young infants are intubated without anaesthesia and in the rare cases in which veins are not accessible intramuscular suxamethonium is used to produce relaxation. For larger children a Ruben or Mitchell nonreturn valve is used; for smaller children and infants a nonreturn system is provided by intermittent digital occlusion of a suitably drilled Rowbotham connector. A specially modified and calibrated E.M.O. inhaler is used to deliver known concentrations of the azeotrope and the patient's lungs are inflated by means of a children's inflating bellows mounted on the standard O.I.B. base (Parkhouse, 1960).

With this technique the tidal volume and minute volume can be measured at any stage by attaching a Wright anemometer to the E.M.O. inlet, due allowance being made for the distensibility of the corrugated tubing. Figure 1 illustrates the complete arrangement of anemometer, inhaler, children's bellows, Rowbotham connector with hole drilled for intermittent positive pressure ventilation and Oxford endotracheal tube.

During maintenance of anaesthesia a change to ventilation with 100 per cent oxygen can be accomplished at any time for diagnostic or other purposes by leading oxygen from a rotameter to the E.M.O. inlet port. Other gases can be added in the same way, so that it is possible to demonstrate shunts either by the nitrous oxide method or by the Valsalva technique. If desired, the

* These are total concentrations, i.e. 0.6 per cent azeotrope indicates 0.4 per cent halothane with 0.2 per cent ether.

FIG. 1
Anaesthetic apparatus used during cardiac catheterization in children. A Wright anemometer is shown at the E.M.O. inlet and the Rowbotham endotracheal connector is drilled to permit intermittent digital occlusion.

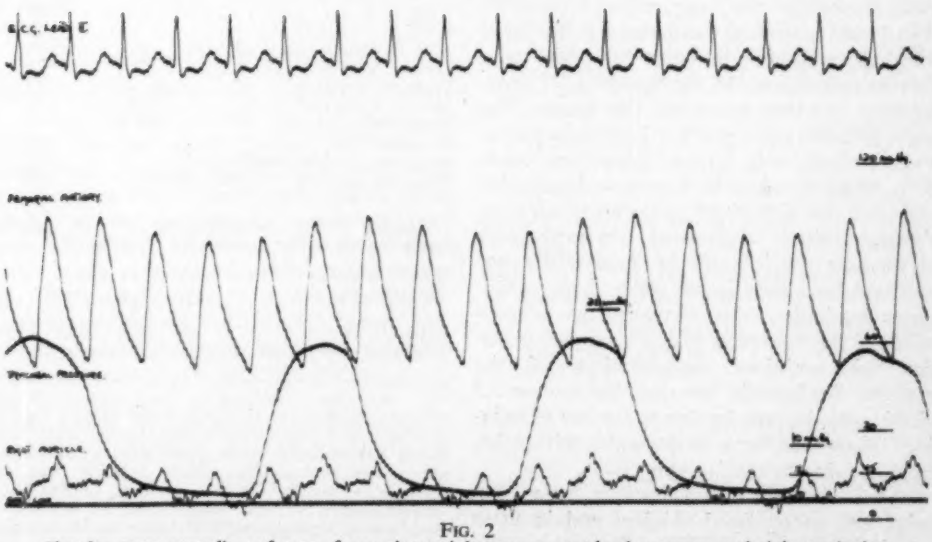

FIG. 2
Simultaneous recording of e.c.g. femoral arterial pressure, tracheal pressure and right auricular pressure during intermittent positive pressure ventilation. Note the absence of significant haemodynamic effects of controlled ventilation. The calibrations (from left to right) are for the tracheal pressure, right auricular pressure, and femoral arterial pressure.

Fick principle for the measurement of cardiac output can be applied by collecting expired air from the nonreturn valve. For this purpose we have found the Ruben valve most convenient. Rapid blood oxygen determinations are made during catheterization by means of a Densitometer and accurate confirmation is subsequently obtained with a spectrophotometer. The minimal concentrations of halothane and ether used in this technique have not caused any significant interference with the results obtained by these methods.

Angiocardiography can be performed at any stage, without delay, the anaesthetist having full control of the patient's respiratory movements during this procedure. Finally, and most important from the point of view of the patient, the anaesthetist is in a position to deal promptly with any complication that may occur.

RESULTS

Azeotrope-air anaesthesia has been administered on 30 occasions for cardiac investigations in children. The age range of the patients has been from 4 weeks to 16 years, and the investigations carried out have included venous angiography, right and left heart catheterization, and angiocardiography. Spontaneous respiration was present throughout the procedure on 2 occasions and in 1 case controlled ventilation was instituted during catheterization in order to obtain more satisfactory conditions. In the remaining 27 cases, respiration has been controlled throughout. The muscle relaxant employed has been intramuscular suxamethonium in 5 cases, intermittent intravenous suxamethonium in 7 cases and gallamine in 17 cases. We have found gallamine much more satisfactory than intermittent suxamethonium and we now use it routinely. Bradycardia was noted in 2 cases early in the series, during spontaneous respiration with relatively high concentrations of the azeotrope. Using controlled ventilation with minimal concentrations of the azeotrope, bradycardia has not been observed and this may, in part, be due to our use of gallamine. There has been 1 death in this series, which was due to cardiac tamponade.

Twelve of the 30 investigations have been carried out on cyanosed children and in these cases it has been possible to demonstrate the presence of intracardiac shunts and to measure any rise in arterial oxygen saturation which may occur when such a patient is ventilated with pure oxygen.

Case 6. This 11-year-old boy was cyanosed when right heart catheterization and angiocardiography were performed. During controlled ventilation with air at 6 l./min, his femoral arterial oxygen saturation was 85 per cent. When ventilated at the same minute volume with 100 per cent oxygen, this arterial saturation rose to 95 per cent. Two weeks later a left heart catheterization was performed on the same child. His condition had deteriorated; his cyanosis was much more marked, and the lungs were noticeably more difficult to inflate. Arterial oxygen saturation in the aorta was 67 per cent during ventilation with air, and 83 per cent during ventilation with oxygen.

As would be expected, ventilation with pure oxygen has been found to make little difference to the arterial oxygen saturation of non-cyanosed patients. Two further cases are summarized below to illustrate the potentialities of the technique.

Case 7. T.L., aged 14 months. Catheterization under azeotrope-air and gallamine with controlled ventilation.

Findings	Pressure	Per cent oxygen saturation
I.V.C.		58*
S.V.C.		61*
Mid. rt. atrium.		68
Low rt. atrium.		78
High rt. ventricle		83
Mid rt. ventricle	60/0	84
Main pulm. art.	60/30	83
Lt. pulm art.		82
Fem. art. (patient breathing air)		91
Fem. art. (patient breathing oxygen)		94

Cardiac output determination by Fick principle, using Ruben valve (controlled ventilation).

Minute volume	=	4.67 l./min
Oxygen uptake	=	72.8 ml/min
R.Q.	=	0.930
Systemic flow	=	1.52 l./min
Pulmonary resistance	=	13.4 units

* It was Fieldman et al. (1955) of the Mayo Clinic who first observed that during catheterization under anaesthesia the superior vena caval oxygen saturation is often higher than that of the inferior vena cava. This is a reversal of the normal finding during catheterization of the unanaesthetized subject and Fieldman et al. suggested that it may be due to reduced oxygen consumption by the brain under anaesthesia.

The large and consistent step-up in oxygen saturation in the region of the tricuspid valve, together with the low systemic blood flow, indicated a diagnosis of ventricular septal defect with considerable left-to-right shunt. This diagnosis was subsequently confirmed at operation and the defect was closed with the aid of extracorporeal circulation.

Case 8. Six-year-old male child with basal systolic murmur and history of severe bronchitis. Catheterization under azeotrope-air and gallamine, with controlled ventilation.

Findings	Pressure	Per cent oxygen saturation
Main pulm. art.		71.8
Lt. pulm. art.		71.0
Pulm "wedge"	9 (Mean)	
Rt. ventricle	25/0	71.0
Rt. atrium	+1/−1	70.0
Aorta	100/70	
Brachial art		96.2

Cardiac output determination by Fick principle, using Ruben valve (controlled ventilation).

Minute volume	=	4.87 l./min
Oxygen uptake	=	154 ml./min
R.Q.	=	0.877
Cardiac output	=	4.0 l./min

The normal oxygen saturations, normal pressures and normal cardiac output in this child indicated absence of any serious cardiac lesion. Central venous pressure and right atrial pressure were within the normal range, despite intermittent positive pressure ventilation.

SUMMARY AND CONCLUSIONS

General anaesthesia has for long been regarded as unsuitable for cardiac catheterization in children because arterial oxygen saturation is altered, and because nitrous oxide and ether interfere with Van Slyke determinations. However, if general anaesthesia is maintained by means of minimal quantities of an anaesthetic vapour added to room air, and if arterial oxygen determinations are made by means of a spectrophotometer or an oximetric method, these objections disappear. This paper describes a technique for the maintenance of light general anaesthesia with intubation and controlled ventilation. The minute volume can be adjusted to any required level and complete immobility of the patient can be ensured with minimal quantities of the anaesthetic agent. In a small series of cases this method of anaesthesia has proved superior to previously used alternatives.

ACKNOWLEDGMENTS

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THE PLACE OF OXYGEN IN SHOCK

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THE Medical Research Council in two Memoranda (1944, 1957) indicate that they regard oxygen as a useful drug to have available for the treatment of shock, but that it plays no vital part in the routine management of the shocked patient.

In experiments to be described it was noticed that the administration of 100 per cent oxygen often produced an apparently beneficial rise in the blood pressure and restored, in varying degrees, Traube-Hering waves to the blood-pressure tracing. In these experiments shock was produced by bleeding into a reservoir and, after a time, returning all the blood to the animal. Thus the animals were not hypovolaemic during oxygen administration. On a number of occasions oxygen would not produce this pressor effect but merely excited the chemorecptor organs, leading to a small drop of 2 to 4 mm Hg in the blood pressure.

The subject of oxygen in shock cannot be considered as closed if only because in practice oxygen is so widely administered in a variety of shock states.

* This work, carried out at the Royal College of Surgeons, was incorporated in an M.S. thesis for the University of London.

METHOD

Irreversible shock was induced in rats by alternate bleetings and retransfusions (Weale, 1958a). Anaesthesia was obtained using intraperitoneal pentobarbitone (4.2 mg/100 g. body weight). One hundred per cent oxygen was administered through a side-connection in the tracheotomy tube during the second 5 minutes of each normovolaemic phase.

Oxygen saturation estimations were carried out prior to shock induction, at the end of the first 5 minutes of each normovolaemic phase, and at the end of the normovolaemic phase when the animal had breathed 100 per cent oxygen for 5 minutes. A spectrophotometric micromethod was employed (Weale, 1960).

RESULTS

Figure 1 shows a typical example of a tracing obtained in an oxygen-sensitive (responsive) rat. As oxygen is administered there is a momentary, chemoreceptor mediated drop in the blood pressure, followed by a sustained rise. This, in its turn, is interrupted by the next haemorrhage. The chemoreceptor mediated drop remains in evidence to the fatal end of the experiment,

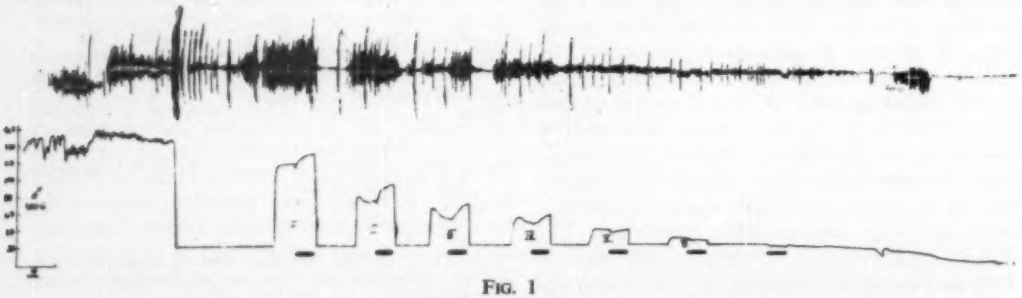

FIG. 1

In some rats oxygen sensitivity can be demonstrated early in shock. The blood-pressure rise later becomes less marked and finally disappears, leaving only the chemoreceptor effect. Upper tracing=respiration; lower tracing=blood pressure. Signal=oxygen. Scale (in this and subsequent figures): ordinate marked off in mutiples of 20 mm Hg; abscissa shows 10-minute interval.

FIG. 2

This animal is oxygen-resistant from the first reinfusion segment onwards.
Signal=oxygen.

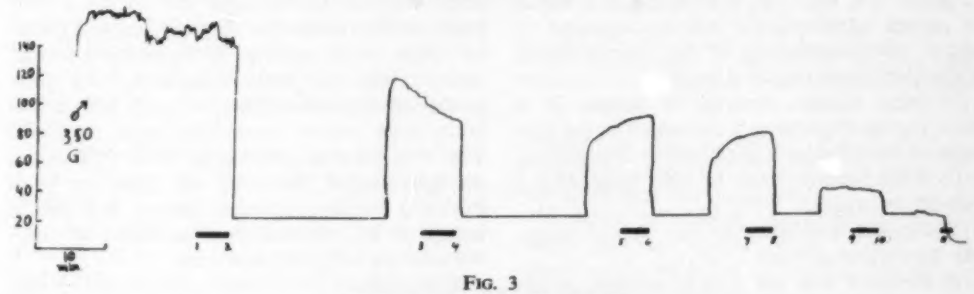

FIG. 3

Oxygen saturations (per cent):

1 = 100	4 = 100	7 = 93	10 = 100
2 = 100	5 = 98	8 = 100	11 = 89 (death)
3 = 93	6 = 100	9 = 97	

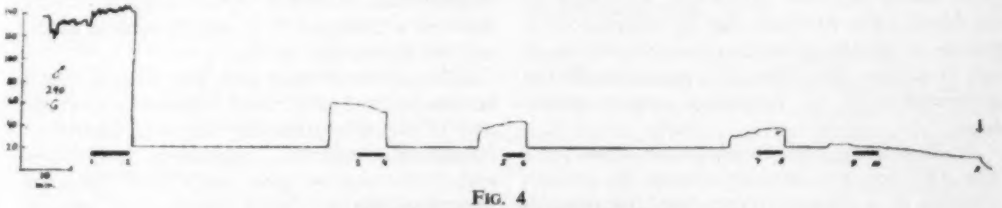

FIG. 4

Oxygen saturations (per cent):

1 = 83	4 = 94	7 = 93	10 = 95
2 = 91	5 = 94	8 = 94	11 = 95 (death)
3 = 88	6 = 98	9 = 96	

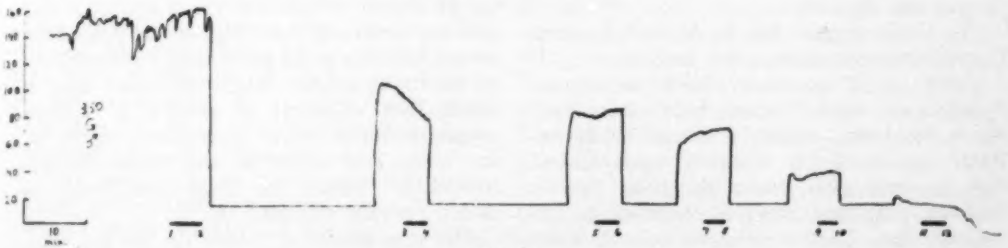

FIG. 5

Oxygen saturations (per cent):

1 = 90	4 = 95	7 = 96	10 = 97
2 = 89	5 = 87	9 = 94	11 = 93
3 = 91	6 = 93	8 = 98	12 = 97

whereas the oxygen initiated pressure elevations become less and less marked until they altogether disappear.

Figure 2 shows the chemoreceptor mediated pressure fall in an oxygen-resistant (unresponsive, insensitive) rat, i.e. one in which this is followed by no rise in the blood pressure.

In any individual rat it was impossible to predict which course the experiment would follow.

Figures 3, 4, and 5 show experiments in which the oxygen administration was accompanied by oxygen micro-estimations of the arterial blood. In summary these results show that:

(1) Some animals respond to oxygen by a rise in the blood pressure, a rise which in the later stages of shock becomes progressively less marked.

(2) Other animals from an early stage do not respond to oxygen.

(3) Oxygen saturation in the control period may be surprisingly low.

(4) However low the arterial oxygen saturation may be and however late a stage of irreversible shock has been reached, it is almost always possible to raise saturation by several per cent.

(5) Whilst increases in oxygen saturation of the blood early in shock may be followed by a pressor response, equivalent rises late in shock fail to achieve this. This is consistent with the presumption of an increasing oxygen resistance.

(6) In those animals in whom the blood pressure does not rise following oxygen, there is no evidence of a reduced oxygen handling capacity of the lungs (see below).

DISCUSSION

Oxygen and the heart.

The results suggest that the Medical Research Council's views require careful analysis.

Firstly, it is necessary clearly to separate hypovolaemic shock ("haemorrhage") from shock which has been adequately treated by the retransfusion of all lost blood. It seems obvious that in most cases where the body fluid is depleted this must first be corrected. In the tracings (fig. 1) the normovolaemic intervals show that although the blood pressure is lower than it had been during the control period, the exhibition of oxygen alone can lead to significant improvement over that which a quantitative restitution of lost blood might achieve. The momentary fall in the blood pressure which occurs when oxygen is first given, because of the speed of the response, is almost certainly the result of a lowering of the total peripheral resistance, itself due to a chemoreceptor mediated reflex. In the early stages of shock this fall, however, may be overcome by a pressor factor, whose speed of response is significantly slower than the reflex referred to. Because the chemoreceptor reflex remains evident to the very end and therefore must imply a partial and prolonged relaxation of the peripheral resistance, the slow permanent rise is most likely to result from action in the other pressure controlling organ, the heart. The slow pressure elevations, when they occur, strongly suggest that they are produced by a gradually increasing cardiac output, and this is indeed to be expected from an organ so notorious for its oxygen dependence.

The evidence for a diminution in cardiac output in shock is so overwhelming (Blalock and Harrison, 1927; Erlanger, Gesell and Gasser; 1919; Hamilton, Dow and Hamilton, 1950; Opdyke and Foreman, 1947; Wiggers, 1942), that few will dispute it. It applies both to hypo-, and normovolaemic shock.

It is not immediately clear why oxygen should become ineffective as shock inexorably proceeds. Any of the five pulmonary function parameters (ventilation, diffusion, pulmonary circulation, and distribution of gases and blood) could be adversely affected for a number of reasons. Disregarding the difficulty of carrying out these tests with accuracy in rats, pulmonary function as a whole would be of interest if, and only if, the transfer of oxygen into the bloodstream was seriously hampered. Some idea of this pulmonary oxygen handling could more easily be ascertained by measuring arterial oxygen saturation after a standardized exposure to oxygen. If arterial oxygen saturation cannot be sufficiently improved, the lungs may easily be the "locus majoris resistentiae" where the progressive block to effective oxygen utilization lay.

The experiments in which the oxygen saturation was measured showed that oxygen enters the bloodstream with undiminished ease, whether it was early or late shock, whether it was an oxygen "sensitive" or oxygen "resistant" animal.

A more detailed investigation into any of the pulmonary function parameters was not, therefore, of first importance. The usefulness of 100 per cent oxygen in raising the arterial saturation is unmistakable.

It was also noted incidentally that cyanosis of the limbs became established long before arterial oxygenation became incomplete. Primarily, therefore, the cyanosis of shock is peripheral. Late in shock some cyanosis of central origin could also be assumed, though this was not to be ascribed to diminished pulmonary oxygen handling. Diminished pulmonary blood flow and shallow respiration are the most likely contributory agents.

If, then, the lungs are not primarily involved in the "block" to effective oxygen utilization, could it be the blood? Again, this is unlikely. The immediate and invariable chemoreceptor effect suggests not only an efficient oxygen transfer mechanism from alveoli to the haemoglobin molecule, but an equally efficient oxygen carriage.

Inevitably, therefore, one is driven back to the conclusion that just as the rise in the pressure tracing upon oxygen administration is most probably cardiac in origin, so the failure for this rise to take place is also most probably cardiac. For reasons not evident at the present moment in some animals the heart ceases to benefit from oxygen in the late stages of shock; in others benefit ceases early.

It might not be unreasonable to conclude that the continuous exhibition of 100 per cent oxygen is routinely indicated were it only for the fact that *some* animals may thereby be assisted. This was done in two preliminary experiments which rather startlingly showed that the expected survival time was almost halved when oxygen was given continuously. A small planned series of ten experiments to investigate this point supported the view that continuous oxygen shortened the survival time (fig. 6).

The reason was not far to seek. When an animal is bled into a reservoir under air to a pressure of 20 mm Hg, the bleeding eventually stops after arterial blood has assumed a dark purple colour. If 100 per cent oxygen is now administered, a flow of bright red blood recommences, indicating that the cardiac function has

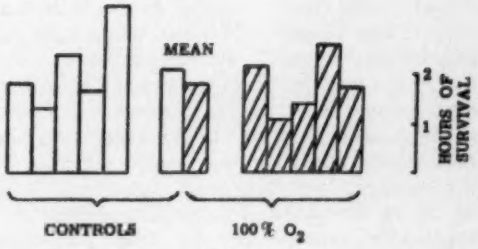

FIG. 6

Ten experiments to test the effect of 100 per cent oxygen upon length of survival in standard shock. With continuous oxygen there is some curtailment.

improved to such an extent as to enable more blood to be pumped out. Continuous oxygen can only accentuate this blood loss.

Certainly in clinical shock where haemorrhage has not finally been quenched the administration of added oxygen may in this way be deleterious. Postoperatively, and in non-haemorrhagic forms of shock and in haemorrhagic shock, when all bleeding is controlled, one cannot conceive how oxygen could have anything but a salutary effect on the heart.

Oxygen and the peripheral resistance.

The chemorecptor mediated depression in the blood pressure focuses attention upon a physiological region which, in recent decades, has been much blamed for the blood-pressure fall in shock. That the peripheral resistance in shock cannot be fully abolished is evident from the fact that the blood pressure can still further be lowered by the administration of oxygen.

Dimunition in cardiac output carries with it certain inevitable consequences of a biophysical nature which suggest, other things being equal, that the peripheral resistance in shock should rise. The studies of Whittaker and Winton (1933), Pappenheimer and Maes (1942) and Green, Lewis and Nickerson (1944) indicate that at slow flows the viscosity of blood rises, thus indirectly raising the total peripheral resistance. Flow hindrance (Lamport, 1955), a term applied to the dimensional factors controlling peripheral resistance, must inevitably be increased when vessels passively constrict as a result both of their elastic walls and the diminished distension due to a lowered blood pressure.

The critical closing pressure to which Burton (Burton and Yamada, 1951) has called attention will, in the very small arterioles, accentuate the rise in the total peripheral resistance due to the other factors. If, in addition, the serum content of fibrinogen rises, as it classically does in haemorrhage, then the sum total of changes in the peripheral resistance must cumulatively add up to an overall increase. Such a theoretically predictable increase in the total peripheral resistance has, in fact, been demonstrated to be the rule (Weale, 1958b), and the effect of oxygen upon it must be negligible.

SUMMARY

In irreversible rat shock it is shown that the animal becomes progressively more refractory to the benefits of oxygen. This is the direct result not of diminished pulmonary function or of changes in the blood but occurs because the oxygen consumption of the heart progressively diminishes.

It is suggested that oxygen can be valuable in nonhaemorrhagic forms of shock and in haemorrhagic shock when all blood has been replaced and haemostasis is complete. With bleeding uncontrolled, oxygen may be harmful.

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THE MYASTHENIC STATE AND THE MYOTONIC SYNDROME*

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MYASTHENIA means undue fatiguability of muscle, myotonia excessive muscle tone, and it is from these opposing manifestations that the two diseases myasthenia gravis and myotonia congenita (Thomsen's disease) are named.

In fact neither myasthenia gravis nor myotonia congenita are isolated diseases. Myasthenia gravis is the most frequently observed aspect of the myasthenic state, by which is meant a state of muscular weakness that is responsive to neostigmine. Myotonia congenita is part of the myotonic syndrome, which forms one group of the muscular dystrophies.

Myasthenia and mytonia have been considered to be pharmacologically contrasting entities (Goodman and Gilman, 1956), the former being due to lack, and the latter to excess, of acetylcholine at the motor endplate. Although modern views of their aetiology do not support this theory, it is still worth while considering the clinical aspects together, as each presents problems to the anaesthetist relative particularly to muscle function.

THE MYASTHENIC STATE

To the anaesthetist the myasthenic state presents three important problems; its recognition, the anaesthetic technique to be employed and the postoperative management.

Clinical manifestations.

Myasthenia gravis: classical; undiagnosed; incorrectly diagnosed; during remission.

Associated with other diseases: thyrotoxicosis; collagen diseases; carcinoma; nutritional.

Iatrogenic: neomycin; streptomycin.

Unknown.

Myasthenia gravis.

The textbook picture of myasthenia gravis, with bilateral ptosis, chin supported on one hand and saliva drooling from the corner of the mouth is easily recognized. But to diagnose the condition is nevertheless difficult in many cases, and failure to do so may lead to embarrassing consequences. Leaming (1959) reported the result of the administration of a moderate dose of d-tubocurarine chloride which required 14 hours active resuscitation. This patient, unknown to the anaesthetist, had been seen some time previously and had been diagnosed as a probable mild myasthenic, on a history of transient attacks of muscular weakness.

It is therefore essential to be familiar with the distribution, the mode of presentation and the natural history of the disease, if similar misfortunes are to be avoided. In a recent study of 60 cases, Garland and Clarke (1956) came to the following conclusions:

The incidence is about 1 in 40,000 which means that there are perhaps 2,000 cases in Great Britain at one time.

The presenting symptom or sign is often solitary. In 25 per cent of cases it is ocular, the patient showing diplopia or ptosis. Generalized asthenia and weakness of the legs are the next commonest complaints.

Advanced cases with multiple signs are often regarded as neurotic, or sometimes as suffering from disseminated sclerosis.

Complete spontaneous remissions frequently occur and these vary in length from a few days to several years. The disease itself may last from 1 to more than 28 years.

Fergusson, Hutchinson and Liversedge (1955) believe that, when myasthenia is localized to the extrinsic eye muscles for two or three years, further involvement is unlikely. However,

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Churchill-Davidson and Richardson's test (1956), using decamethonium iodide, supports the view that the disease is generalized, and not limited to the clinically affected muscles. Also Querido (1929) found at postmortem perivascular foci of leucocytes, lymphocytes, plasma cells and fibroblasts in skeletal and myocardial muscle, as well as in liver, lungs and kidneys. He believed myasthenia gravis to be a generalized vascular disease.

Myasthenia associated with other diseases.

There is a peculiar relationship between thyrotoxicosis and myasthenia. Approximately 5 per cent of patients suffering from myasthenia gravis become hyperthyroid and several instances are recorded of hyperthyroidism preceding or coinciding with the onset of myasthenia gravis (Millikan and Haynes, 1953). A "see-saw" effect has been described between the two diseases, the muscular weakness becoming apparently relieved by the onset of thyrotoxicosis and becoming worse again when treatment with antithyroid drugs is instituted. In both acute and chronic thyrotoxic myopathy, neostigmine has proved beneficial (Laurent, 1944; Sheldon and Walker, 1946). In one case myasthenia disappeared after thyroidectomy (Sheldon and Walker, 1946).

The muscular weakness and fatiguability seen in certain collagen diseases have responded to neostigmine therapy. References having been made to polymyositis (Reese and Harman, 1954; Christensen and Levison, 1950), dermatomyositis (Bonduelle, Bouygues and Coulon, 1955), and systemic lupus erythematosis (Harvey et al., 1954).

Croft (1958) described 5 patients with carcinoma who also exhibited myasthenic features. Although Gray (1958) and others have criticized the evidence, there is no doubt that neurological disorders associated with neoplasia unrelated to the central nervous system do occur. Hensen, Russell and Wilkinson (1954) found 4 instances of myasthenia in a review of 19 patients with malignant disease and a coincident neurological disorder, even though subacute cerebellar degeneration is said to be the most frequent occurrence. Other writers have noted a similar association, the primary growth being usually bronchial, although growths in the breast, ovary, sigmoid colon and prostate have been implicated.

Symptoms and signs resembling those of classical myasthenia can also occur in cases of long-standing nutritional deficiency (Musselman, 1945; Katz, 1946).

Iatrogenic myasthenia.

With regard to the antibiotic drugs forming the iatrogenic group, Pittinger, Long and Miller (1958) reported a case of prolonged neuromuscular block in a patient treated with neomycin, and Loder and Walker (1959) described a myasthenic-like reaction in association with the use of streptomycin.

Myasthenia of unrecognized aetiology.

Occasionally cases that defy diagnosis occur in which myasthenic features predominate. One, known to the author, had an acute onset of muscular weakness which initially responded to neostigmine, but which progressed to the extent that tracheostomy and intermittent positive pressure respiration became life-saving measures.

The myasthenic state, therefore, may be due to a diversity of causes, although myasthenia gravis in its many guises is the commonest. Unfortunately in spite of pharmacological and electromyographic tests a clear diagnosis is not always possible. Every effort should be made, once suspicion has been aroused, to reach such a diagnosis, since on this will depend the anaesthetic technique.

Anaesthetic Technique.

Little has been written about anaesthesia and myasthenia gravis except in relation to thymectomy. In the past, some of the recommendations seemed likely to jeopardize rather than improve the patient's chances of survival. These included:

The maintenance of anaesthesia without endotracheal intubation lest the postoperative tracheitis should prove disastrous.

The withholding of intravenous fluids during and after operation, for fear of increasing tracheal and bronchial secretions.

The administration of 5 per cent carbon dioxide postoperatively, as a prophylactic measure against pulmonary collapse.

It may be profitable, therefore, to examine critically some desiderata for an "ideal general

anaesthetic" for thymectomy, in a patient suffering from myasthenia gravis. From this it is possible to make such minor modifications as may be dictated by circumstance, when a myasthenic state exists in patients requiring anaesthesia for some unrelated condition.

Such essential considerations as the absence of pre-operative upper respiratory tract infection, the use of blood transfusion and controlled respiration are not peculiar to anaesthesia for thymectomy. They are routine in any major thoracic operation, and will not be discussed further.

Preparation.

Patients with myasthenia gravis, who are receiving anticholinesterase drugs orally, can be controlled more effectively and accurately with neostigmine given by injection. This is analogous to the use of soluble, instead of "lente" preparations of insulin.

Premedication.

The drugs used for premedication should be carefully selected to control secretions and to allay anxiety. The secretions may be excessive due to the anticholinesterase drugs already in use and since hyoscine is a superior antisialogogue to atropine (Wyant and Dobkin, 1957) it is preferable. Advanced cases of myasthenia may have diminished respiratory function, hence any marked depression of the respiratory centre by sedatives must be avoided. Slaughter (1950) has shown that neostigmine potentiates morphine and other analgesics commonly used for premedication. If this is so, there is a place for the recently developed ataractic drugs as alternatives.

Anaesthesia.

A sleep dose of thiopentone for induction and intubation, followed by maintenance using nitrous oxide and oxygen is said to be all that is required. However, Adams and Parkhouse (1959) doubt this on clinical grounds and suggest the use of halothane or of the azeotropic mixture of diethyl ether and halothane. Either provides a non-explosive adjuvant to nitrous oxide, without the use of relaxant drugs, so making intubation easier and the course of anaesthesia more tranquil.

An alternative suggestion (Gray, 1959) is to omit the final pre-operative dose of neostigmine, thus making the patient's respiration easier to control by virtue of the existing muscle weakness.

The alleged ease of intubation has been attributed to an abnormal sensitivity of the myoneural junction to the curariform effects of thiopentone and, although experimental evidence for this is slender (Comroe, Dripps, Bothello and Metz, 1947), the degree of muscle relaxation resembles that produced by suxamethonium in normal patients (Dundee, 1956). Adams and Parkhouse, and Dundee, are correct in their observations, since the resulting relaxation depends on the degree of myasthenia which varies from case to case, and at different times in the same patient.

The use of muscle relaxant drugs is not essential, as even in resistant myasthenics, the addition of low concentrations of halothane allows respiration to be easily controlled. Indeed muscle relaxants are contra-indicated, as those belonging to the nondepolarizing group cause prolonged paralysis of the myoneural junction. Those of the depolarizing group may produce a dual response at an abnormal motor endplate. The use of drugs under conditions in which they might produce an abnormal response even in the smallest dosage is not good practice, when similar results can be achieved by other drugs that have little or no effect on the motor endplate.

Many of the problems involved in anaesthetizing patients in the myasthenic state can, however, be eliminated, if a local analgesic technique is employed. Where feasible, local analgesia is to be preferred but care in the choice of the premedication and the management of post-operative analgesia remain important.

Postoperative Management

Increased doses of neostigmine by injection may be required, but "pharmacological juggling" must never be allowed to hide the main point at issue, namely, the establishment of adequate pulmonary ventilation. A so-called crisis should be treated by the use of tracheostomy and intermittent positive pressure ventilation, without the addition of further neostigmine which can itself produce neuromuscular blockade.

Successful management by this method has been reported by Jorgenson and Therkelson (1954), and by Chang, Harland and Graves

(1957). Churchill-Davidson and Richardson (1957) considered that recovery might be attributable to rest of the motor endplate. They carried their theory to its logical conclusion by completely paralyzing with d-tubocurarine chloride a patient who had passed into a myasthenic crisis and maintained artificial respiration for eight days. At the end of this time a dramatic improvement took place. Similar results, in 3 out of 4 cases, have also been reported by Most van Spijk and Lammers (1957) who curarized their patients for only 24 hours and their results, although less dramatic, were definitely encouraging.

If then, there is any doubt as to the efficiency of respiration during the postoperative period, in spite of increased doses of neostigmine, artificial pulmonary ventilation is the essential of successful management.

THE MYOTONIC SYNDROME

Myotonia congenita and the closely related conditions of paramyotonia and dystrophia myotonica form the myotonic syndrome, the presenting feature of which is excessive muscle tone. The anaesthetist's attention to dystrophia myotonica has been drawn by Dundee's report (1952) of an abnormal response to thiopentone. As the myotonic syndrome forms but one group of the muscular dystrophies it seems logical to examine them as a whole, and to pay particular attention to those that constitute the syndrome.

Classification

The muscular dystrophies, or myopathies, can be defined as a group of diseases in which voluntary muscle undergoes a primary degeneration that is not subsequent to any demonstrable lesion of the nervous system. Nineteen different types have been described, but Walton and Nattrass (1954) classify them in three main groups,* two definite clinical subgroups and the myotonic syndrome.

Main groups:

(1) Duchenne type of muscular dystrophy.

(2) Fascio-scapulo-humeral muscular dystrophy.

(3) Limb-girdle muscular dystrophy.

Clinical subgroups.

Distal type.

Occular.

Myotonic syndrome.

Dystrophia myotonica.

Myotonia congenita.

Paramytonia.

Main groups.

Of the three main groups, the second, in which there is little disability, is unlikely to present the anaesthetist with any particular problems. But the other two, where there is widespread involvement, and in which death usually occurs from respiratory failure, set the same problems as any disease that results in severely diminished respiratory function of muscular origin, such as anterior poliomyelitis, or Landry's paralysis.

When respiratory function is only just adequate to support the life of the patient, many factors can precipitate respiratory failure. The commonest is probably acute infection and here the assistance of the anaesthetist may be required in the medical ward (Shackleton, 1958). Anaesthesia, or its side effects, can be precipitating factors in two ways, either by depression of the respiratory centre with various drugs, which diminish the effective drive, or by neuromuscular block affecting the muscles of respiration. In such cases a diminished tidal volume, especially in the postoperative period, may lead to respiratory failure more certainly and rapidly than in normal patients.

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* *The three main groups of muscular dystrophies.*

The Duchenne type occurs usually in males before the age of 3 years, symmetrically involving the pelvic girdle and spreading within 3–5 years to shoulder girdle, with pseudohypertrophy particularly of calf muscles in 80 per cent. Steady rapid progression with gross deformities leading to death by inanition or respiratory failure between 10 and 20 years of age.

Fascio-scapulo-humeral type affects both sexes at any age, involving, sometimes asymmetrically, those muscles after which it is named, and spreading in 20–30 years to the pelvic girdle. Slow progress with periods of arrest result in slight deformity, and most survive, remaining active to a normal age.

Limb-girdle type appears in both sexes from late in the first to the third decade, beginning either in pelvic or shoulder girdle. The dystrophy is frequently asymmetrical when first involving shoulder muscles, and spreads to the unaffected girdle muscles in 20 years. A variable rate of progression results in severe disablement with deformities in late stages and death by middle age.

Bearing these mechanisms in mind, a local analgesic technique may be the most suitable. Where a general anaesthetic is essential, the author believes that premedication should consist of atropine only (4.65 mg). Thiopentone, if used at all for induction, must be strictly limited (100–150 mg). Anaesthesia should be maintained using inhalational agents, with assisted respiration where necessary. Relaxant drugs should be avoided, as in certain circumstances both depolarizing and non-depolarizing groups may have residual effects; (Brennan 1956; Zaimis, 1959). The postoperative medication should be minimal.

Clinical subgroups.

In the two clinical subgroups, the pathological processes, by definition, remain localized for many years and the respiratory muscles are not involved. Hence no special problems relating to anaesthesia are likely to be encountered.

Myotonic syndrome.

The syndrome is composed of three entities of which dystrophia myotonica is the basis. Myotonia congenita (Thomsen's disease) is a congenital form of dystrophia myotonica in which dystrophic features have not yet occurred. (Maas and Peterson, 1950). Paramyotonia is a rare condition in which myotonia is precipitated only by exposure to cold. It is possible that this kind of mechanism may play a part in the failure of some infants to restart respiration after prolonged surgery, usually thoracic, where heat loss has been marked and where a spontaneous fall in body temperature has occurred.

Diagnosis.

The clinical aspects of dystrophia myotonica have been summarized by Walshe (1944) as "a heredo-familial disease characterized by wasting of the digital muscles of the limbs, sternomastoids and certain fascial muscles, a peculiar delayed relaxation of muscles, by testicular atrophy, baldness, cataract and mental deterioration". Other and more detailed accounts can be found in current text books of neurology and in various papers (Bell, 1947; Maas and Peterson, 1950; DeJong, 1954).

As with myasthenia gravis, the classical case is relatively easily recognized (fig. 1) and many of these patients will volunteer that "something is wrong with my muscles". The most striking physical sign of dystrophia myotonica is the patient's inability to let go after shaking hands.

FIG. 1

A typical case of dystropria myotonica.

(Reproduced from figure 43 of *Diseases of the Nervous System, by* F. M. R. Walshe, by kind permission of the publishers, E. and S. Livingstone, Ltd.)

FIG. 2

A recent case of the author's

Female, aged 36, admitted for total hysterectomy. No relevant past history or abnormalities noted at routine pre-operative examination. Weight about 45 kg.

Premedication. Pethidine 50 mg, hyoscine 0.5 mg.

Anaesthetic. Thiopentone 300 mg; d-Tubocurarine chloride 20 mg; pethidine 80 mg; nitrous oxide and oxygen. Intubated and respiration controlled using circle absorption for 1½ hours.

Postoperative course. 10.30 a.m. Still apnoeic after 0.65 mg atropine +2.5 mg neostigmine I.V.

10.38 a.m. Atropine + neostigmine repeated.

10.50 a.m. Nalorphine 5 mg repeated once I.V.

11.00 a.m. Shallow respirations began, respiration assisted with nitrous oxide and oxygen—total flow 8 l./min.

12.20 p.m. Respiration adequate.

Following day. Close questioning and detailed examination revealed: Clumsy in movement for past 15 years, difficult in getting on and off buses for past two years. Myotonic grip. Weak and atrophic neck muscles, quadriceps, tibialis anterior and perineal muscles of both legs. Fine peripheral dust-like opacities seen on slit lamp examination of lens.

An electrographic tracing may be made in suspected cases, thus demonstrating the undulating, "rain-shower-like" electrical oscillations first described by Eichlet and van Hattingberg (1938), and which are diagnostic of myotonia.

Action of thiopentone.

Dundee (1952) described two patients who had been given thiopentone for the induction of anaesthesia and he noted an undue depression of respiration in both. Subsequently he investigated one volunteer in whom 50 mg of thiopentone caused an abnormal respiratory depression. From this and other indirect pharmacological evidence Dundee stated, "considering that a constant finding in patients with this disease is an abnormality of the muscles themselves, it is reasonable to conclude that their muscles are hypersensitive to the action of thiopentone".

Bourne and Zuck (1957) reported a similar response in one patient, and later investigated the same case, when they noted respiratory depression with both 50 mg of thiopentone and 10 mg of pethidine. Langton Hewer (1957) observed 40 minutes apnoea following 100 mg thiopentone. In spite of these clinical findings there is no direct evidence, as yet published to support the initial premise that the muscles are unduly sensitive to thiopentone.

Since pethidine produces a similar response to thiopentone a specific sensitivity to the barbiturate is an unlikely cause of the respiratory depression. Also the author's patient (see fig. 2 and special note) began to breathe again only after a central antagonist to pethidine had been administered.

It is therefore possible, although the evidence is still only that of clinical observation, that undue sensitivity of the respiratory centre to drugs which have a depressant action, particularly thiopentone, might cause the respiratory depression previously observed. In support of this theory it should be remembered that many cases of dystrophia myotonica show a marked dystrophic element with generalized wasting (Walton and Natrass, 1954). Dundee (1956) stated that with thiopentone the dose/weight relationship is only obvious at extremes of body weight; but Herman and Wood (1952) found that a 5 per cent decrease in the body fat of rats resulted in a 100 per cent increase in the length of anaesthesia. Clinical experience shows that a reduced dose of thiopentone should be used in wasted individuals as they are deprived of the buffering mechanism of body fat (Keating, 1956).

It would be interesting to investigate in patients with this disease the effect of other drugs, which depress respiration. Until further information is available, however, the cause of this response to thiopentone remains obscure and all that can be said is that thiopentone is contra-indicated in patients suffering from dystrophia myotonica.

Anaesthesia.

If general anaesthesia is essential, a similar technique to that described for the other myopathies should be employed, with the reservation that thiopentone must not be used. Local analgesia may be considered preferable in order to minimize central depression, even though the myotonic element will remain unaffected (Kennedy and Wolf, 1948; Bucthal and Clemmensen, 1941).

This discussion about a rare disease may seem of no great practical importance, but an examination of the notes of the Department of Neurology at Oxford reveals that, in the past 10 years, 23 cases of the myotonic syndrome have been seen, 8 of whom were resident within the city boundary. Also, it is worth recording that in the past year 2 of these patients have had general anaesthetics without mishap. In both cases induction and maintenance were achieved using inhalational agents only.

Hence without engaging on any statistical estimations, it is justifiable to say that, although the myotonic syndrome is rare, the anaesthetist should consider the possibility that such cases may come under his care and are not merely "text book curios".

SUMMARY

In this paper an attempt has been made to bring to light certain lesser known aspects of two so-called rare diseases. They interest the anaesthetist not only from the standpoint of their theoretical pharmacology but also by virtue of their clinical manifestations which have a direct bearing on the conduct of anaesthesia. Obviously, both for the patient's well-being and incidentally for re-

search purposes, patients in the myasthenic state and with the myotonic syndrome ought to be anaesthetized at centres where there are adequate facilities for diagnosis and postoperative supervision.

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THE EVOLUTION OF ANAESTHESIA

3. THE ANAESTHETIC FACEPIECE AND EARLIER MASKS

BY

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To many people the facemask is symbolic of anaesthesia and indeed it is only in comparatively recent times, with the increasing popularity of spinal and other injection methods, that anaesthetic agents have been introduced by other means. But several months were to elapse between the discovery of the anaesthetic properties of ether and the invention of the facemask for its inhalation, although very good ones were in use for gaseous inhalation fifty years before. However, since the vogue of pneumatic medicine had waned considerably in the intervening years (Slatter, 1960a) it is not surprising that in the excitement of trying out the new discovery, these masks were forgotten, the apparatus for anaesthesia being based instead on the contemporary steam inhalers and the gasbags of the recent "Frolics."

The majority of ether inhalers invented in the early weeks of 1847 utilized the long flexible breathing-tube with the "speaking-trumpet" mouthpiece of the steam inhalers and gasbags of the period. Behind the mouthpiece was a box containing cedar-wood or cork ball valves to prevent the return of expired air into the apparatus. The mouthpiece itself consisted of a central tube to be held between the lips, with a cup-shaped pad which was pressed tightly round them. Sometimes the central tube was lacking. The nostrils were pinched closed by the fingers of the administrator or by a spring clip. Natural breathing was thus made impossible and in many cases the ether vapour was inhaled only with great difficulty. Frequent failures were recorded.

Tracy's Mouth-pad, February 1847. One of the many inhalers exhibited at the Pharmacological Society's Meeting on January 13, 1847, was the glass apparatus of S. J. Tracy of St. Bartholomew's Hospital (1847a, d). Its only remarkable feature was its curious shape—"it bears some resemblance to a German pipe" (Tracy, 1847b) (fig. 1).

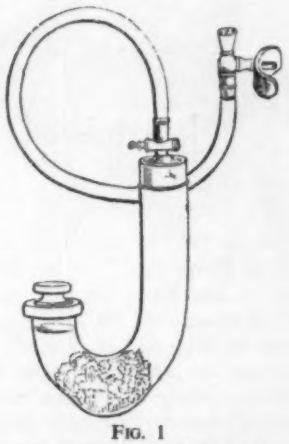

FIG. 1
Tracy's ether inhaler, 1847.

In use, however, Tracy found that the valves would not act unless "the patient's head was raised and the valve-piece became perpendicular". So he separated it from the mouthpiece by inserting between them an extra piece of flexible tubing about 4 inches long. He also designed a new type of mouthpad. This was formed of "10 to 12 thicknesses of flannel and covered with morocco". It was about 5½ inches long and 4 inches wide. The mouth-tube was "screwed into the mount, over which a piece of vulcanized rubber larger than the pad with a hole in the centre is placed. The person who administers the vapour can easily press this on the patient's mouth, and compress the nose with the same." (1847c).

Snow's Inhalers, March, April and September 1847. Snow was always ready to make improvements to his apparatus. Figure 2 shows what may be called his Model II. Model I made at the end of January, had an ordinary mouthpiece and valve-box combined (Snow, 1847a) but for

FIG. 2
Snow's ether inhaler (Model II), 1847.

Model II Snow (1847b) had adopted the new mouth-pad of Tracy (figs. 2, 9, 10, 11). He had also added a regulating stopcock, so that the amount of air mixed with the ether vapour might be increased or decreased at pleasure. Although they were not yet available, Snow was "now getting elastic tubes, valves and mouth-tubes, made purposely for the apparatus three-quarters of an inch in diameter". He had discovered that great restriction to breathing was caused by the narrow inhaling-tubes and, by taking the inner diameter of the human trachea as the criterion of bore, he was able to avoid this unnecessary difficulty.

In April, Model III, "a small and very neat apparatus" to be carried in the pocket, made its appearance (Snow, 1847c). It was a smaller edition of Model II. By dispensing with the pipe surrounding the inhaler and by substituting flat for spherical valves and a ferrule for the stopcock, it could be packed into "a round leather case, such as is commonly used for holding cupping glasses". Model IV (fig. 3) was depicted in Snow's book published in September (1847d). The inhaler rested in a large metal box which served both as a water-bath and a container for the breathing-tube and facepiece.

Ether as an anaesthetic was quite new in 1847, though it had frequently been used in the previous century as an antispasmodic and light analgesic for the relief of headaches, tic douloureux and so on (Slatter, 1960b). In the years immediately prior to the discovery of anaesthesia these applications had been neglected; they were, however, revived to a moderate extent with the new interest in ether. Francis Sibson, surgeon at the General Hospital, Nottingham, using a somewhat modified version of Snow's spiral inhaler, employed ether to cut short the paroxysms of facial neuralgia and allow the patient temporary relief from his pain. There was the usual difficulty in maintaining inhalation with semiconscious patients, and Sibson also had to contend with the special complication that some of his patients suffered with convulsive tic in the face,

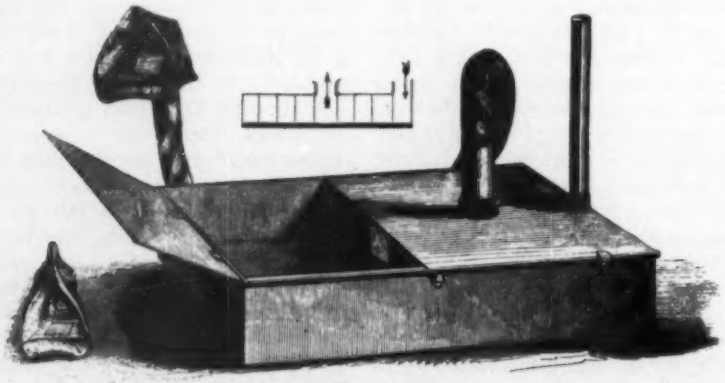

FIG. 3
Snow's ether inhaler (Model IV) and face-piece, 1847.

and could not use the mouthpiece at all. On the suggestion of another surgeon of the hospital, Sibson constructed a nose-and-mouthpiece to overcome this.

Sibson's Nose-and-mouthpiece, February 1847. He bought "a common sixpenny mask" from which he cut out the septum of the nose and lips. He lined it inside with oiled silk and "pasted a funnel of Macintosh cloth over the nose and mouth, and over this a piece of Macintosh to go over the cheeks". It was held in place by a rubber strap and buckle and pressed against the nostrils with the fingers (fig. 4). He had tried it on "a remarkably lantern jawed shrivelled old man, a crying boy, on several girls", and in all cases with complete success.

This mask was used for some time by Snow, but he thought that strapping it to the head was unsafe as fresh air could not then be given quickly to a patient in an emergency. By making a mask moulded to the contours of the face and by transferring the valves from the tube on to it, Snow adapted Sibson's nose-and-mouthpiece into the prototype of the anaesthetic facemask of today.

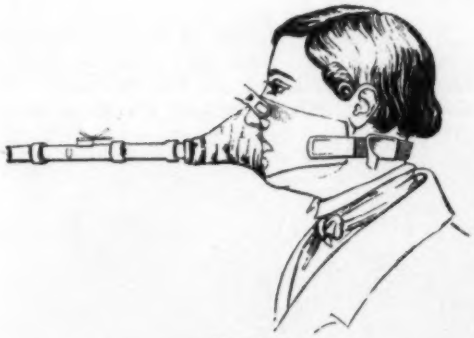

FIG. 4
Sibson's nose and mouth-piece, 1847.

Snow's Facepiece, June (1847d). It was made of thin sheet-lead "the pliability of which admits of its being easily adapted to the peculiar form of the features", covered with silk or glove-leather and lined with oiled silk. The central part was of brass, iron or plated copper and contained the rubber flap-valves. The expiratory valve was made "to turn on a pivot, so as to allow of the admission of external air, and to supersede the use of a ferrule or two-way tap" (fig. 5). From that time the facemask became a standard piece of anaesthetic equipment, and it is the only survivor into modern times of these early anaesthetic inhalers.

The dotted lines indicate the position of the expiratory valve when turned aside for the admission of unvaporized air.

FIG. 5
Snow's face-piece, 1847.

In 1774 Priestley made his "surprise" discovery of oxygen. After some preliminary tests with mice, he had the "curiosity" to breathe the gas himself. Its effect on him confirmed his belief of its "superior goodness" and he expressed the view that "pure dephlogisticated air might be very useful as a medicine" (quoted Slatter, 1960a). Within a few years the use of oxygen for treating disease had become widespread both in this country and on the Continent. François Chaussier of Dijon—"one of the most distinguished physicians of that [eighteenth] century"—taking into account the "vital" properties of the gas, concluded that a proper use of it would be for the resuscitation of infants, born in an asphyxiated condition (*Dict. Encyclo. Sci. Med.*, 1874). It had long been the practice to attempt insufflation of the lungs in these cases, but although the idea was good, the usual means employed were not. Mouth-to-mouth inflation

filled the lungs with vitiated and harmful expired air, while the use of household bellows was dirty. Chaussier therefore "constructed a very simple apparatus" for this purpose by means of which oxygen could be administered "with ease and safety". It included a complete facepiece.

Chaussier's Apparatus and Facepiece, c. 1780. The facepiece, "a sort of funnel or horn" of bladder, covered both nose and mouth (fig. 6, C).

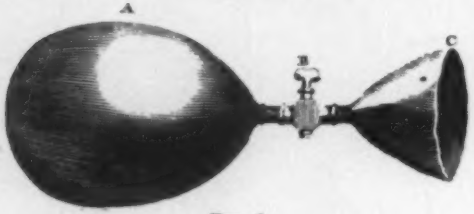

FIG. 6
Chaussier's apparatus, *c.*1780.

FIG. 7
Chaussier's apparatus, *c.*1780.

It could easily be moulded to the features and was held on with the fingers. Adhesive plaster or a ribbon round the head of the patient were other means of keeping it on. The stop-cock was opened and oxygen squeezed from the large bladder (A) into the lungs. Chaussier (1785) had used this apparatus with good results to relieve a young man suffering from advanced consumption, but had not actually had the opportunity to try it for resuscitation. Another apparatus for the treatment of chest diseases is shown in figure 7. Oxygen was contained in the "large glass globe" (AB) submerged in the "little tub" (G) of hot or cold water. This rose up into the globe as the oxygen was breathed. The facepiece (F) of this apparatus had a soft cushioned rim.

Chaussier thought it desirable that a supply of oxygen should be kept at all Rescue Stations, and that practitioners should have it in readiness at every difficult confinement. He said: "The prudent accoucheur should prepare in advance all the means proper to the restoration of life" and particularly should he use oxygen, for Chaussier anticipated that more success would come of this than from any other method hitherto employed.

A very similar facepiece to that of Chaussier was used a few years later by Dr. Robert Menzies of Edinburgh, for his experiments on tidal volume. His dissertation *De Respiratione* (1790) contained "experiments made with the greatest degree of accuracy" and which "together

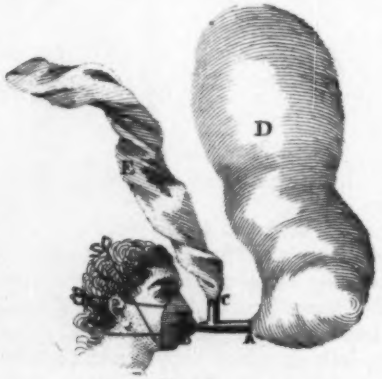

FIG. 8
Menzies' apparatus, 1790.

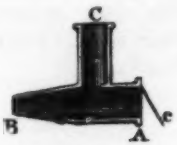

FIG. 9
Menzies' apparatus, 1790.

with the importance of the subject" was "sufficient excuse for giving it to the public in an English dress" six years later. Menzies took up previous work on respiration and tried to copy the experiments, but finding obvious disadvantages in the old methods, he designed some new equipment for himself.

Menzies' Apparatus, 1790. He took "two pretty large tubes joined together at right angles" to which he tied two allantoid membranes (fig. 8). He breathed air from E into D by means of two very light flap-valves of allantoid (fig. 9, c) which directed the flow in the tubes.

Christopher Girtanner of Göttingen, being, like Beddoes, both chemist and physician, followed the work of the latter with great interest and applied the methods himself. He made the justifiable criticisms that Beddoes' case histories (Beddoes and Watts, 1794) were not sufficiently accurate, that he did not properly define the different kinds of consumptive diseases and that he used the many different gases indiscriminately. Girtanner selected carbonic acid gas (carbon dioxide) to treat lung diseases; its pain-killing properties were well known, and on account of its heavy weight he believed it would sink to the bottom of the lungs and not be expired again immediately. His attention had been drawn to Menzies' apparatus as a suitable device by which the gas might be inhaled, but he found that the patients hated the strings which held it on and, as well as that, the valves were not reliable.

Girtanner's Inhaler and Mask, 1795. Based on Menzies', the apparatus (figs. 10, 11) consisted of two tubes joined at right angles to each other, containing valves. These rested on inclined seats (fig. 11, b, c). A bladder of gas was tied on at c. Girtanner pointed out that the inspiratory valve (fig. 11, c) was incorrectly drawn as it should open inwards instead of outwards. "The mask consists of a hemisphere of thin brass which is furnished with a stuffed leather pad." It was to be pressed closely to the face and it even had an indentation for the bridge of the nose. Each apparatus was supplied with three different sizes of "mask", so that every patient might have a well-fitting one.

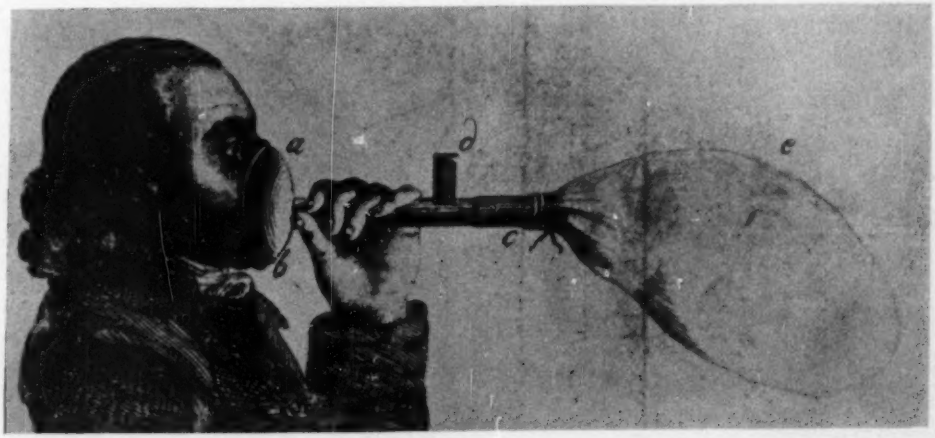

FIG. 10
Girtanner's inhaler and masks, 1795.

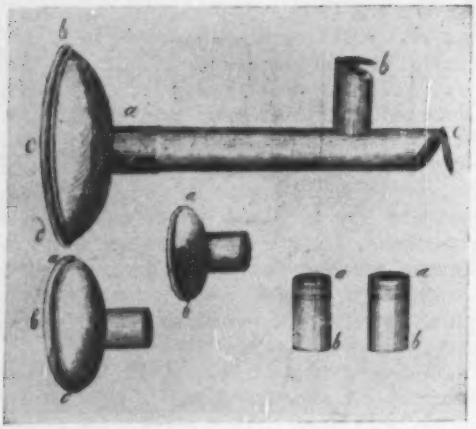

Fig. 11
Girtanner's inhaler and masks, 1795.

Girtanner called this apparatus an "inhaler". He claimed that everybody who tried it approved of it and that experience showed it to be preferable by far to other types of apparatus. It was, in fact, the "best, most convenient and most suitable" instrument for the purpose then to be had (*J. pract. Arznk.*, 1795).

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